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Complementary Medicine Products Used in Autism - Evidence for Rationale

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1. Introduction

The use of complementary and alternative medicine (CAM) is increasing in children with chronic illness or disability (Mamtani&Cimino 2002; Ernst 2005; Hyman&Levy 2005; Sinha&Efron 2005). Generally, the term CAM includes complementary therapies, such as behavioural/physical therapies, in addition to products such as herbals and vitamins that are administered systemically. This study specifically considers CAM products and supplements. Prevalence of biologically-based CAM product use in children with autism spectrum disorder (ASD) is among the highest of any population, with reported lifetime use of between 35% and 70% (Hanson et al. 2007; Christon et al. 2010; Green et al. 2006; Senel 2010). High CAM usage in autism has been attributed to the availability of few conventional pharmacological treatments that have a limited evidence base and are often associated with significant adverse effects.

Recent well-designed studies using whole-genome scanning methods, cytogenetics and genetic linkage/association analyses indicate genetic factors play a key role in the aetiology of autism (Eapen, 2011). Environmental and epigenetic factors have also been shown to impact on susceptibility to autism (Persico&Bourgeron 2006). Evidence is building that autism represents a cluster of syndromes that have distinct aetiologies involving inflammation, increased oxidative stress, impaired gastrointestinal (GI) health, mitochondrial dysfunction, autoimmune processes, and impaired ability to neutralise toxins (London 2007).

There is a belief that CAM products may ameliorate biological abnormalities that are reported to occur in autism. Reasons cited by parents for using CAM products for their children with autism include general health maintenance as well as specific symptoms such as moodiness, aggression, irritability, hyperactivity, inattention, GI symptoms, and sleep difficulties (Wong&Smith 2006). Another reason commonly cited by caregivers for implementing CAM products is that sensory processing difficulties and aberrant behaviour that can occur in children with autism may lead to poor feeding patterns and the possibility of nutritional deficiencies (Geraghty et al. 2010).

A study by Golnik and Ireland (2009) surveyed 539 medical practitioners (19% response rate using email and regular post) regarding CAM use in children with autism. The study

revealed physicians encouraged use of multi-vitamins (49%), PUFAs (25%), melatonin (25%) and probiotics (19%) in children with autism and discouraged use of chelation (61%) and secretin (43%). In the same study medical practitioners responded positively when asked if they desired more complementary alternative medicine training for these patients (Golnik&Ireland 2009).

Despite this widespread use of CAM products in children with autism, it is of concern that there is a distinct lack of accurate, unbiased and evidence-based information about CAMs available for health professionals and caregivers of children with autism. Ready access to information through the Internet has contributed to the general increased frequency of caregivers implementing CAMs (Hyman&Levy 2005). Families perceive CAMs as a risk-free approach that may improve their child's outcome (Hyman&Levy 2005). However, all treatments used in children should be judged on standards of scientific research (Levy&Hyman 2003). Studies supporting CAM usage in autism need to be evaluated for scientific study design, clinical safety and scientific validity (Levy&Hyman 2003). There have been few published reviews examining the evidence for rationale, safety and efficacy of CAM products in autism (Angley et al. 2007; Weber&Newmark 2007; Levy&Hyman 2008; Atkins et al. 2010), and none were conducted systematically. To address this gap, we have endeavoured to address this area systematically in this chapter.

This chapter presents the first part of a two-part review. The rationale for a range of CAM products that are used in the management of autism is examined in this chapter. It is hoped this information will inform researchers and health care professionals about the theoretical or proven basis for a range of CAM products used in autism.

Chapter 4 which is the second part of the two-part review includes an examination of 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 a specific CAM product has been investigated in autism have been examined.

2. Aim

To systematically review the literature to determine the rationale of a range of CAM products used in ASD. 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 and thiamine tetrahydrofuryl disulphide), metallothionein promotion, glutathione and glutamine.

3. Method

For part 1 of this 2-part review (i.e. Chapter 3), a generalised review of the literature was performed to examine the possible rationale behind the use of these CAMs in ASD which included locating articles describing and investigating the biological basis of autism. Cross-sectional studies investigating biochemical abnormalities that occur in autism were also retrieved. For part 2, (i.e. Chapter 4) randomised controlled trials or randomised cross-over

Topic	Search Terms
<i>Calcium</i>	Calcium/, calcium.mp, bone meal.mp
<i>Chelation/Allithiamine/TTFD/DMSA</i>	chelating agent\$.mp, ttf.d.mp, tetrahydrofurfuryl disulfide.mp, allithiamine.mp, Chelating Agents/, Chelation Therapy/, Thiamine/, Garlic/ dimercaptosuccinic acid.mp, dmsa.mp
<i>Colostrum</i>	colostrum.mp, Colostrum/
<i>Dimethylglycine</i>	dimethylglycine.mp, DMG.mp
<i>Enzyme therapy</i>	Enzymes/, Peptide hydrolases/, Pancrelipase/, Lipase/, Amylases/, gastrointestinal agents/, proteolytic enzyme\$.mp., enzyme\$.mp., pancreatic enzyme\$.mp., enzyme therapy.mp., carboxyl peptidase.mp.,
<i>Fatty acids</i>	Fatty Acids, Essential/, Fish Oils/, Docosahexaenoic Acids/, Fatty Acids, Omega-3/, Cod Liver Oil/, Fatty Acids, Unsaturated/, Eicosapentaenoic Acid/ Fatty Acids, Omega-6/, gamma-Linolenic Acid/, Linoleic Acid/, Evening Primrose/, Onagraceae/, Oenothera/, essential fatty acid.mp, fish oil.mp, docosahexaenoic acid.mp, omega 3.mp, w-3 fatty acid.mp, cod liver oil.mp, marine oil.mp, menhaden oil.mp, highly unsaturated fatty acid.mp, eicosapentaenoic acid.mp, evening primrose oil.mp, fever plant.mp, gamma linolenic acid.mp, linoleic acid.mp, night willow herb.mp, primrose.mp, sun drop.mp, onagraceae.mp, oenothera\$.mp
<i>Iron</i>	Iron/, Ferrous Compounds/, iron.mp, ferrous\$.mp.
<i>L-glutamine</i>	Glutamine/, l-glutamine.mp, glutamine.mp
<i>Magnesium</i>	Magnesium/, Magnesium Compounds, magnesium.mp.
<i>Melatonin</i>	Melatonin/, melatonin.mp
<i>Metallothionein</i>	metallothionein.mp, mt promoter.mp, metallothionein promoter.mp, Metallothionein/
<i>Olive leaf extract</i>	Olea/, Olive/, olive lea\$.mp., olea.mp., oleuropein.mp., olea europaea.mp.

Topic	Search Terms
<i>Probiotics</i>	Probiotics/, Probiotic/, Yogurt/, Lactobacillus/, Bifidobacterium/, probiotic\$.mp., yeast.mp., microbes.mp., yogurt.mp., yoghurt.mp. flora.mp.,lactobacillus.mp.,candidiasis.mp., saccharomyces.mp., bifidobacteria.mp., acidophilus.
<i>Reduced l-glutathione</i>	reduced glutathione.mp, glutathione.mp, Glutathione/
<i>Selenium</i>	Selenium.mp, Selenium/, Selenium Compounds
<i>Secretin</i>	Secretin/, secretin.mp
<i>Vitamins</i>	Vitamin A/, Retinoids/, vitamin A.mp, retino\$.mp, Fat-soluble vitamin\$.mp, water soluble vitamin\$.mp., Ascorbic Acid/, vitamin B6.mp, pyridoxine.mp, Vitamin B 6/, Pyridoxine/, Vitamin B 6 deficiency/, folic acid.mp, folinic acid.mp, folate.mp, vitamin B9.mp, Folic Acid/, Leucovorin/, Folic Acid Deficiency/, Vitamin B Complex/, vitamin B12.mp, cyanocobalamin.mp, methylcobalamin.mp, Vitamin B 12/, vitamin C.mp, ascorbic acid.mp, ascorbate.mp, ascorbyl\$.mp. Vitamin E/, Tocopherols/, Tocotrienols/, vitamin E.mp, tocopherol.mp, tocotrienol.mp.
<i>Zinc</i>	zinc.mp, Zn.mp, Zinc/

/ at the end of a term denotes a subject heading in MEDLINE, AMED or CINAHL. Some subject headings differ between these databases.

In some databases the symbol \$ is used to truncate a word, in some databases the symbol * is used instead

Table 1. Search terms used in database searches.

trials in which participants served as their own controls, were used to assess effectiveness of specific CAMs in individuals with ASD. Clinical trials of all designs were used to examine reported adverse effects of the CAMs in this population.

For the purposes of this review, the term CAM was used only in reference to non-conventional medications, sometimes termed 'biological treatments' or 'dietary supplements' (Levy&Hyman 2005) used in ASD, but not other forms of complementary or alternative therapy (e.g. touch therapies, manipulation therapies). Off-label use of prescription medications was not considered in this review.

The list of CAM products selected for review was developed using previous literature reporting CAM products being implemented by caregivers in their children with autism (Green et al. 2006; Wong&Smith 2006; Hanson et al. 2007; Christon et al. 2010) and consensus amongst authors based on our own research experiences.

Computerised literature searches were performed to locate articles reporting clinical trials of CAMs in children or adults with ASD. The databases searched were Medline (via Ovid), EMBASE, International Pharmaceutical Abstracts (IPA), Allied and Complementary Medicine (AMED), CINAHL, the Natural Medicines Comprehensive Database (Therapeutic Research Faculty) and The Cochrane Library.

To search for articles relevant to ASD standardised search terms were used including: *autis\$.mp*, *Asperger\$.mp*, *developmental disabilit\$.mp*, *pervasive developmental disorder\$.mp* (as key words); and *Autistic Disorder/*, *Asperger Syndrome/*, *Child Development Disorders/*, *Developmental Disabilities/*, *Speech Disorders/*, *Child Psychiatry/* *Communication Disorders/*, *Language Disorders* (as subject headings).

These terms were combined with other terms to identify articles on specific CAMs as indicated in Table 1. Studies were restricted to English language. Searches were restricted to the years 1970 to December 2010. The reference lists of published studies and systematic reviews were also checked for relevant articles.

For the Natural Medicines Comprehensive Database the Product Effectiveness Checker was used to search for articles examining effectiveness for autism or Asperger Syndrome.

4. Results

4.1 Rationale

CAM product usage in autism generally has a theoretical basis rather than a proven rationale. However, there are some instances where biochemical abnormalities have been demonstrated in studies which can be normalised with administration of CAM products. For example James et al. (2004) showed biomarkers of oxidative stress in children with autism could be normalised following supplementation with betaine, folic acid and vitamin B12. Some studies have also examined how the effects of biochemical normalisation translate into quantifiable outcome measures of behaviour in autism.

The rationale for the use of the CAM products investigated was found to fall into one or more of the following categories: promote GI health, reduce oxidative stress, enhance detoxification of heavy metals, modulate the immune system, normalise neurotransmitter abnormalities, promote sleep and prevent or treat nutritional deficiencies. The theoretical or proven abnormality occurring in autism, rationale for the CAM products investigated and behaviour targeted where known are summarised in Table 2.

4.1.1 Promotion of gastrointestinal health

A high frequency of GI disturbance occurring in individuals with autism was first reported almost 40 years ago (Goodwin et al. 1971), but data regarding prevalence are conflicting. High rates of functional gastrointestinal disorders (FGIDs) in individuals with ASD have been reported in several studies including abdominal pain, constipation, diarrhoea, diarrhoea and alternating constipation and GI inflammation (Horvath et al. 1999; Molloy&Manning-Courtney 2003; Levy et al. 2007). A prospective study by Valicenti-McDermott et al. reported an increased prevalence of GI conditions in children with ASD (n=50, 70%) compared with matched controls that included both neurotypical children (n=50, 28%) and those with non-ASD developmental disorders (n=50, 42%) (2006). However, a recent well-designed population-based study by Ibrahim et al. found that the overall incidence of GI symptoms did not differ between cases of autism and controls (2009).

Recently Campbell et al. have provided genetic evidence supporting the link between GI dysfunction and autism and reported an association between a single nucleotide polymorphism in the promoter of the mesenchymal epithelial transition (MET) factor gene and autism (2009). Evidence is also emerging that intestinal permeability (D'Eufemia et al. 1996; Horvath et al. 1999; de Magistris et al. 2010), GI mucosal inflammation (de Magistris et al. 2010), fermentation products (Yap et al. 2010) and GI microbiota profiles (Finegold et al. 2002; Song et al. 2004; Parracho et al. 2005; Finegold et al. 2010) in individuals with autism are different from those of the general population.

4.1.1.1 Intestinal hyper-permeability in autism

Functional changes have been reported in the GI tracts of children with autism including increased intestinal permeability (Horvath&Perman 2002). Intestinal permeability, as measured by the urinary excretion of metabolically inert sugars, is a surrogate marker of mucosal integrity and gut barrier function (de Magistris et al. 2010). It has been hypothesised that impaired GI function may not only be a symptom of autism but may also contribute to the phenotypic presentation by increasing absorption of chemicals from the GI tract. There is a body of thought that increased absorption of opioid-like peptides that are derived from gluten and casein (i.e. the 'opioid excess theory') may disturb neurological function, as may GI overgrowth of neurotoxin-producing bacteria (Shattock&Whiteley 2002).

4.1.1.2 Altered gut fermentation products in autism

A growing appreciation for the role of intestinal microflora in health and disease has emerged over the last few years, however the beneficial and potentially adverse contributions of bacterial fermentation by-products have not been well established and are largely uncharacterised in children with ASD. A recent metabonomic study revealed metabolic phenotype (metabotype) differences were observed between autistic and control children, which were associated with perturbations in the relative patterns of urinary mammalian microbial co-metabolites including dimethylamine, hippurate, and phenylacetylglutamine (Yap et al. 2010). Another study by Altieri et al. (2011) found higher levels of p-cresol in urine of young children with autism than controls and also reported a positive correlation between urinary p-cresol and autism severity. P-cresol is a toxic metabolite of tyrosine catabolism by gut bacteria such as clostridial species and *Pseudomonas stutzeri* (Altieri et al. 2011). Whether the observed differences in urinary metabolites observed contribute to, or reflect, GI dysfunction in individuals with ASD requires further investigation.

4.1.1.3 Altered GI microbiota profiles in autism

Several studies have found some bacterial species, particularly some *Clostridium* species, are present in higher numbers in children with autism experiencing GI disturbance (Finegold et al. 2002; Song et al. 2004; Parracho et al. 2005; Finegold et al. 2010). Some workers have speculated that the differences in the GI microbiota could be contributing to the pathophysiology of ASD (Bolte 1998; Finegold 2008).

4.1.1.4 Altered digestive enzyme capacity in autism

It has been hypothesised that digestion of dietary gluten and casein in the small intestine by pancreatic and intestinal peptidases releases short chain peptide molecules (exorphins) which are structurally similar to endogenous opioid substances (White 2003). Other

hypotheses suggest that excessive opioid activity linked with dietary peptides from gluten and casein have an aetiological role in the pathogenesis of autism (Reichelt&Knivsberg 2003). The 'opioid excess' theory of autism proposes that many of the behaviours found in individuals with ASD mimic the influence of opioids on human brain function (White 2003). In addition Horvath & Perman (2002) demonstrated that 44 of 90 (49%) of children with autism showed at least one deficient disaccharidase enzyme activity. Lactase and maltase were the enzymes most commonly measured to have deficient activity, followed by sucrase, palatinase and glucoamylase. They found that all of the children with reduced enzyme activity had flatulence and/or loose stools. It is hypothesised that disaccharide malabsorption may cause chronic diarrhoea and flatulence in children with ASD and may contribute to abnormal behaviour (Patel et al. 2002). Hence, supplementation with these enzymes may cause a reduction in autism related symptoms. For example supplementation with lactase may resolve the symptoms related to lactose malabsorption (Horvath&Perman 2002).

It is speculated that GI symptoms exacerbate the behavioural manifestations of autism contributing to the severity of the disorder (Buie et al. 2010). Abdominal pain, constipation, and/or diarrhoea are unpleasant and can be painful and likely to produce frustration, behavioural problems, and possibly sleep disturbance, aggression and self abuse, especially in children unable to communicate their discomfort.

Various CAMs are used to ameliorate the GI symptoms in children with autism as outlined in Table 2. Probiotics and prebiotics are used to promote gut health. Dietary interventions include the exclusion of gluten and casein containing foods together with dietary supplementation with peptidase enzymes. Peptidase enzymes are implemented in children with autism in an attempt to remove the opioid-like peptides that may exert a neurotoxic effect on the brain (Brudnak et al. 2002). Less obvious candidates are PUFAs which are used with the rationale that they can decrease GI inflammation and improve a 'leaky gut'.

4.1.2 Oxidative stress

A leading theory implicated in the aetiology of autism is oxidative stress, which results from a complex interplay of genetic and environmental factors. Oxidative stress occurs when reactive oxygen species (ROS) levels exceed the antioxidant capacity of a cell leading to damage and functional impairment (McGinnis 2004). "It is thought that autism could result from an interaction between genetic and environmental factors with oxidative stress as a potential mechanism linking the two" (Ming et al. 2005, p.379). These ROS target lipids, proteins and nucleic acids (Chauhan&Chauhan 2006) resulting in a risk of neurologic deficits, especially during early life (Zecavati&Spence 2009). A range of evidence has emerged in recent years supporting the role of oxidative stress in the aetiology of autism.

4.1.2.1 Lipid peroxidation

It has also been found that lipid peroxidation (an oxidative biomarker) in plasma is significantly increased in children with autism when compared to their non-autistic siblings reflecting increased oxidative stress in autism (Chauhan et al. 2004).

4.1.2.2 Antioxidants

Reduced endogenous antioxidant capacity i.e. low levels of the plasma antioxidant enzymes glutathione peroxidase and superoxide dismutase have been found in autistic individuals (Sogut et al. 2003). Furthermore, Yorbik et al. (2002) found that the activities of erythrocyte

superoxide dismutase and erythrocyte and plasma glutathione peroxidase were significantly lower in 45 autistic children compared with 41 controls. Chauhan et al. (2004) also found a significant reduction of the major endogenous antioxidants transferrin and ceroplasmin in the serum of children with autism as compared to their typically developing siblings. An excess of toxic free radicals e.g. nitric oxide has also been reported in children with autism as compared to age and sex matched controls (Sogut et al. 2003). Ming et al. (2005) also describe increased nitrite concentrations, thiobarbituric acid reactive substances and xanthine oxidase activity in red blood cells in children with autism compared to controls. Notably, decreased plasma levels of the antioxidant vitamins A, C and E were reported in the same autistic cohort (Ming et al. 2005).

4.1.2.3 Mitochondrial disease

Mitochondria serve a primary role in energy production during normal physiological function and generate high levels of ROS which are normally neutralised by free radical scavengers. In the event there is excess ROS relative to the antioxidant defence, mitochondrial dysfunction occurs exacerbating oxidative stress. Mitochondrial disease is associated with impaired neurodevelopment. Two recent studies have reported mitochondrial dysfunction in autism. Post-mortem samples showed increased mitochondrial metabolism and oxidised mitochondrial proteins in the brains of six people with autism compared with controls (Palmieri et al. 2010). Another study showed that 11/21 patients with ASD had definite mitochondrial disease while the rest had probable mitochondrial disease (Weissman et al. 2008).

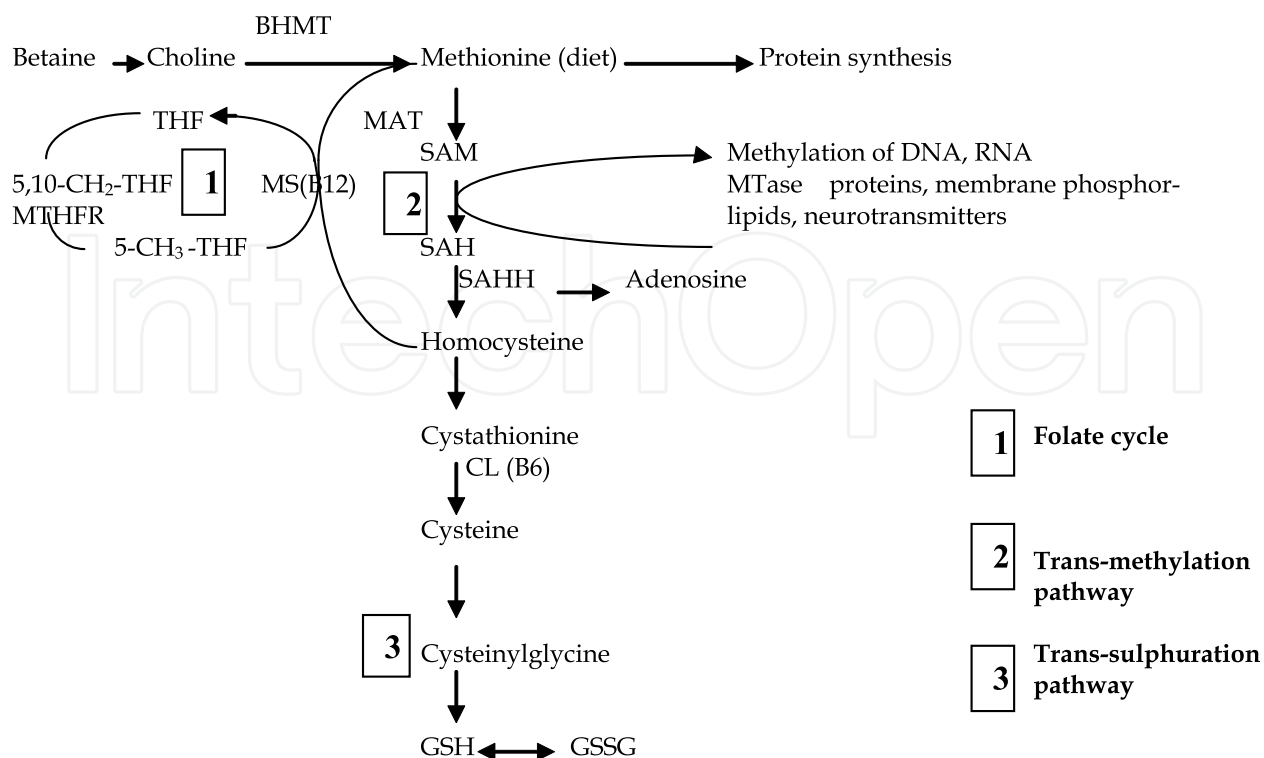
4.1.2.4 Abnormalities in the trans-methylation and trans-sulphuration pathways

There is emerging evidence that a deficient trans-methylation (i.e. folate/methionine) pathway has a role in the aetiology of autism (Boris et al. 2004; James et al. 2004; James et al. 2006). The folate/methionine pathway (Figure 1) is responsible for the synthesis of the deoxynucleotide triphosphate (dNTP) pools required for DNA synthesis and repair, the establishment and maintenance of stable DNA methylation patterns for tissue-specific gene expression and chromatin conformation and maintenance of the redox balance within each cell.

As shown in Figure 1, the methionine cycle involves the re-methylation of homocysteine to methionine either by methionine synthase (MS) which is folate and vitamin B12 dependent or by the betaine homocysteine methyltransferase (BHMT) reaction. The methyl group is donated by 5-methyl tetrahydrofolate synthesised by methylene tetrahydrofolate (MTHFR) from 5,10 methyl tetrahydrofolate.

Methionine is activated by methionine adenosyl transferase (MAT) to S-adenosyl-methionine (SAM), the major methyl donor for cellular methyltransferase reactions (MTases). Following methyl transfer, SAM is converted to S-adenosylhomocysteine (SAH). This is further metabolised in a reversible reaction to homocysteine and adenosine. Adenosine is either phosphorylated to adenosine nucleotides by adenosine kinase (AK) or catabolised to inosine by adenosine deaminase (ADA). Homocysteine may be permanently removed from the methionine cycle by irreversible conversion to cystathionine by cystathione- β -synthase (C β S). Cystathionine is converted to cysteine which is the rate-limiting amino acid for the synthesis of glutathione.

A decrease in turnover of the folate/methionine pathway will lead to decreased synthesis of SAM which is vital for normal methylation activity and decreased synthesis of cysteine and glutathione required for normal antioxidant activity.



Source: Ms P.A.E. Main, 2011. Used with permission

Metabolites THF: tetrahydrofolate; SAM: S-adenosyl-methionine; SAH: S-adenosyl-homocysteine; GSH: reduced active glutathione; GSSG: oxidised disulfide form of glutathione

Enzymes MS: methionine synthase; BHMT : Betaine homocysteine methyltransferase; MAT: methionine adenosyl transferase; SAHH: SAH hydroxylase; C&S: Cystathione- β -synthase; CL: Cystathione lyase; MTHFR: methylene-tetra-hydrofolate reductase; MTRR: methionine synthase reductase

Fig. 1. Folate cycle and the trans-methylation and trans-sulphuration pathways

A systematic literature review identifying studies reporting metabolites, co-factors or genes of the folate/methionine pathway in autism found there are significant differences in the levels of various metabolites of the methionine/folate cycle in individuals with autism compared with controls although there are some inconsistencies between studies which may be due to different methodologies (Main et al. 2010).

Elevated levels of oxidised GSH and subsequent reduction in GSH:GSSG ratio together with a decrease in cysteine (a rate limiting amino acid for glutathione synthesis) and increased lipid peroxidation suggests that oxidative stress may play a significant role in the aetiology of autism (James et al. 2004; Wu et al. 2004). The conclusion of a review of oxidative pathways as potential drug targets in autism by Villagonzalo et al. (2010) was that although there is significant evidence demonstrating that oxidative pathways are disturbed in autism, there is insufficient evidence to decide whether oxidative stress is the cause of autism, or contributes to the illness, or is simply a consequence of the illness. They stated that further research is required to determine if children will benefit from antioxidant treatment and that longitudinal studies exploring oxidative biomarkers and autism symptomatology over time may be a methodology for investigation.

Thus as outlined in Table 2, oxidative stress in autism provides a rationale for the use of CAM products that are antioxidants in their own right, metabolites or co-factors of the trans-methylation or trans-sulphuration pathways, co-factors of plasma antioxidant enzymes and include: vitamins A, C & E, vitamin B12, DMG, magnesium, selenium, zinc, melatonin and glutathione.

4.1.3 Heavy metal toxicity

Heavy metals, such as arsenic, lead, and mercury have been associated with a variety of neurologic deficits and disorders, including lower IQ, Alzheimer's disease, and Parkinson's disease (Zecavati&Spence 2009). It has been suggested that some children with autism have an increased body-burden of mercury which may result from biochemical and genomic susceptibilities within detoxification pathways (Mutter et al. 2005).

As mentioned above James et al. (2004) found a significantly reduced GSH: GSSG ratio in children with autism compared with controls. An impaired glutathione redox ratio is thought to play a role in the aetiology of autism by delaying the clearance of heavy metals from the body (Deth et al. 2008). The association between heavy metal exposure and autism, in particular mercury, has attracted considerable interest (Counter et al. 2002; Holmes et al. 2003; Palmer et al. 2006; Geier&Geier 2007). Mercury has been implicated in immune, sensory, neurological, motor, and behavioural dysfunction resulting in clinical manifestations similar to those defining or associated with autism. Some studies have suggested that mercury can disrupt neurotransmitter levels and biochemistry (Faustman et al. 2000; Redwood et al. 2001; Bernard et al. 2002) and impact on normal child development. A suspected source of mercury is thiomersal, a preservative used in vaccines. Notably, although thiomersal has not been included in US vaccines since 2000, autism prevalence rates have continued to rise (Fombonne 2008).

As shown in Table 2, CAM products that are implemented based on the rationale that autism is associated with heavy metal toxicity include probiotics, allithiamine/TTFD, DMSA, metallothionein promoter, glutathione and glutamine.

4.1.4 Immune dysregulation in autism

There is evidence to suggest the immune system plays a role in the aetiology of autism (Kidd 2002a). It is hypothesised that some cases of autism are associated with immune factors and that autism related symptoms may be associated with immune deficiencies or autoimmunity (Levy&Hyman 2005). Immunological anomalies involving cytokines, immunoglobulins, inflammation, and cellular activation have been reported in individuals with autism (Goines&Van de Water 2010).

4.1.4.1 Immune deficiencies and autism

Immune deficiencies in children with ASD have been reported due to frequently encountered medical problems including recurrent ear infection/rhinosinusitis/upper respiratory tract infection, adverse reactions to multiple medications, allergies, GI problems and prolonged courses of illness as compared to typically developing siblings (Jyonouchi et al. 2005; Levy&Hyman 2005). Various immune system deficits including abnormalities in cell-mediated immunity have been reported in autism. Abnormalities of macrophages, B cells, T cells and natural killer cells have been reported in individuals with ASD which may compromise defence against infection (Gupta 2000).

4.1.4.2 Autoimmune disease and autism

A survey administered to families of 61 children with autism and 46 control families with typically developing children discovered that the mean number of autoimmune disorders was greater in families who had children with autism (Comi et al. 1999). In this study, Comi et al. (1999) found that 46% of the families of children with autism had two or more family members with autoimmune disorders (e.g. type 1 diabetes, adult rheumatoid arthritis and hypothyroidism). In addition, this finding may further suggest that genetic predisposition plays an important role in autism. However, Micali, Chakrabarti & Fombonne (2004) did not have the same findings following administration of a semi-structured questionnaire to 79 parents of children with pervasive developmental disorders (PDDs) and 61 controls (parents with typically developing children). They found the rates for any autoimmune disorder for both mothers and fathers combined was 22.4% for parents of controls and 30.9% for parents of children with PDDs which was not significantly different.

It is hypothesised that autoimmune disease in autism may lead to neurodevelopmental damage. Autoantibodies against proteins associated with the central nervous system (CNS) has been reported in some children with autism (Singh et al. 1988; Plioplys et al. 1994; Vojdani et al. 2004). In recent studies, antibodies against the fetal brain have been detected in some mothers of children with autism; these antibodies have the ability to alter behavioural outcomes in the offspring of animal models (Enstrom et al. 2009).

A review by Theoharides et al (2008) proposes a relationship between GI factors, oxidative stress and immune dysregulation and proposes potential drug targets in autism.

4.1.4.3 Vaccination and autism

Although an array of epidemiological studies do not support causality (DeStefano 2007; Baker 2008), the alleged link between autism and vaccination has been debated extensively and many parents and parent advocacy groups continue to suspect that vaccines cause autism. Putative mechanisms for vaccine associated autism include: "1) immune response directed towards a vaccine that cross reacts with host antigens, 2) host response to a vaccine that would result in the production of cytokines and a subsequent autoimmune reaction and 3) toxic components of a vaccine that directly impact on the immune or nervous system" (Levy&Hyman 2005, p.134).

Therefore as outlined in Table 2, immune dysfunction in autism provides a rationale for the use of CAM products that are claimed to be immunomodulators/immunoadjuvants and include: vitamin A, DMG, vitamin C, zinc, colostrum and glutamine.

4.1.5 Normalise neurotransmitters and neurotransmitter metabolites

Many studies (Young et al. 1978; Garnier et al. 1986; Launay et al. 1987; Minderaa et al. 1987; Barthelemy et al. 1988; Garreau et al. 1988; Barthelemy et al. 1989; Minderaa et al. 1989; Martineau et al. 1991; Martineau et al. 1992; Herault et al. 1993; Martineau et al. 1994; Minderaa et al. 1994; Herault et al. 1996; Croonenberghs et al. 2000; Mulder et al. 2005; Mulder et al. 2005; Mulder et al. 2009) have focused on neurotransmitter abnormalities in individuals with autism. Abnormalities in various neurotransmitters have been implicated in the development of autism, including serotonin (5-hydroxytryptamine, 5-HT), dopamine (DA), noradrenaline (NA), gamma-aminobutyric acid, glutamate and neuropeptides.

4.1.5.1 Serotonin and metabolites

5-HT is a monoamine neurotransmitter that plays an important role in the developing brain by directing both neuronal proliferation and maturation (McDougle et al. 2005). CNS 5-HT activity has been involved in a range of physiological functions, such as sleep, sensory perception and appetite, which are often disrupted in autism (Young et al. 1982). High levels of 5-HT during early development may cause a loss of 5-HT receptors and therefore impact on subsequent neuronal development (Whitaker-Azmitia 2001). Neuroimaging studies suggest altered developmental regulation of 5-HT synthesis may be associated with the pathogenesis of autism (Chugani et al. 1999). Hyperserotonemia has been consistently reported in people with autism in more than 25 published studies (Lam et al. 2006).

4.1.5.2 Dopamine and metabolites

Dopamine (DA) is a catecholamine which acts as a major neurotransmitter in the brain. Generally, the dopaminergic system is thought to affect a wide range of functions, including cognition and attention (Nieoullon 2002), motor function (Niimi et al. 2009), predictive reward signal mechanisms (Schultz 1998) and immunity (Basu&Dasgupta 2000). Some animal research has shown that stereotypies and hyperactivity can be induced by increasing dopaminergic functioning suggesting dopaminergic neurons may be overactive in autism (Miller et al. 2010).

4.1.5.3 Noradrenaline

Noradrenaline (NA) is synthesized from DA by dopamine β -hydroxylase and released from noradrenergic neurons as well as from the adrenal medulla into the bloodstream. NA plays a critical role in attention, the stress response (i.e. the “fight or flight” response), anxiety, and memory (Amaral&Sinnamon 1977; Fitzgerald 2009), which are frequently observed to be impaired in individuals with autism. Previous studies have shown that measurements of NA (i.e. in plasma and urine) are generally well correlated with measurements in the CNS (Roy et al. 1988). A range of neurochemical studies have attempted to examine excretion of urinary NA and / or adrenaline (A) in individuals with autism compared with controls and have yielded inconsistent findings. Three studies found higher levels of NA and/or A in autism compared to controls (Barthelemy et al. 1988; Herault et al. 1993; Martineau et al. 1994), while four studies found no differences (Launay et al. 1987; Martineau et al. 1992; Minderaa et al. 1994; Croonenberghs et al. 2000).

Therefore as outlined in Table 2, the range of neurotransmitter abnormalities that have been shown to occur in autism provide a rationale for the use of CAM products that are claim to normalise neurotransmitter levels and function such as: high dose pyridoxine and magnesium, metabolites and co-factors of the transmethylation and trans-sulphuration cycles (see Figure 1), vitamin C, zinc and secretin.

4.1.6 Sleep

Sleep problems in children with ASD are common with a prevalence of 44-83% in comparison to 10-20% of typically developing young children (Wright et al. 2011). Sleep difficulties contribute to significant morbidity in children and to family stress. Melatonin is a hormone that is synthesised in the pineal gland from the precursor tryptophan. Its production is light-sensitive, beginning in the early evening and reaching peak levels at approximately 3am. Daytime secretion of melatonin is generally insignificant (Jan et al.

1999). The main functions of melatonin within the body are the synchronisation of circadian rhythm and control of sleep patterns and endocrine secretions (Natural Medicines Comprehensive Database 2011). The suprachiasmatic nucleus of the anterior hypothalamus is responsible for the generation of circadian rhythm. Transmission of light through the retina activates this tissue, causing either inhibition or stimulation of melatonin synthesis in the pineal gland. Sleep induction is thought to occur as a result of direct inhibition of the 'wakefulness generating system' by melatonin (Jan et al. 1999).

Two studies have suggested a tendency for autistic children to be deficient in the essential amino acid tryptophan, a precursor in the biosynthesis of melatonin (D'Eufemia et al. 1995; Arnold et al. 2003). Additionally, Tordjman et al. (2005) found a significantly lower excretion rate of 6-sulphatoxymelatonin, the prominent metabolite of melatonin, in children with autistic disorder compared to sex and age-matched controls. These results support the above hypothesis that children with autism may have impaired synthesis of melatonin. Therefore, in theory, supplementation with melatonin could potentially improve their quality of sleep and hence also their daytime behaviour.

4.1.7 Nutritional deficiencies

Factors that contribute to nutritional concerns and deficiencies in children with autism are summarised by Geraghty et al. (2010) and include sensory processing difficulties, rituals and routines and non-compliance behaviours at meal times. Significantly lower levels of nutrients in blood, hair, and other tissues have been seen in autistic children including low levels of magnesium (Strambi et al. 2006), iron (Latif et al. 2002), zinc (Yorbik et al. 2004), vitamins A, C and E, (Ming et al. 2005) and polyunsaturated fatty acids (PUFAs) (Vancassel et al. 2001; Bell et al. 2004; Meguid et al. 2008). Further, medications prescribed for children with autism may have nutrition related adverse effects and restrictive diets that are frequently implemented in autism may compromise nutritional intake. As a result, caregivers may elect to implement CAM interventions to treat or prevent nutritional deficiencies.

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
Vitamin A	Hippocampal retinoid receptor dysfunction Immune system dysfunction (Goines&Van de Water 2010) Oxidative stress (Villagonzalo et al. 2010) Deficiency (Clark et al. 1993; Steinemann &Christiansen 1998; Ming et al. 2005)	Reconnect retinoid receptor pathways (Megson 2000) Immunomodulation (Megson 2000) Antioxidant (Natural Medicines Comprehensive Database 2011) Prevent or treat deficiency	General autistic behaviours

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
Pyridoxine (vitamin B6) and magnesium	<p>Dysfunctional pyridoxine metabolism (Adams&Holloway 2004; Adams et al. 2006)</p> <p>Oxidative stress (Villagonzalo et al. 2010)</p> <p>Magnesium deficiency (Strambi et al. 2006)</p>	<p>Normalise neurotransmitter synthesis (Kidd 2002b; Levy&Hyman 2005)</p> <p>Magnesium is synergistic with pyridoxine (Abraham et al. 1981)</p> <p>Magnesium protects against oxidative damage via activation of CNS copper-zinc superoxide dismutase (CuZnSOD) (Johnson 2001)</p> <p>Magnesium is necessary for many cellular metabolic processes and transmission of nerve and muscle potentials (Natural Medicines Comprehensive Database 2011)</p>	<p>Repetitive behaviour</p> <p>General autistic behaviours</p>
Cyanocobalamin (vitamin B12)	<p>Gut dysbiosis and inflammation results in decreased GI synthesis of B12 and/or absorption (Kidd 2002b; Erickson et al. 2005)</p> <p>Trans-methylation and trans-sulphation pathway abnormalities (James et al. 2004; Bertoglio et al. 2010) causing oxidative stress (Villagonzalo et al. 2010)</p>	<p>Normalise B12 levels (Bertoglio et al. 2010)</p> <p>Correct folate/methionine metabolite profile and other indexes of oxidative stress (James et al. 2004; James et al. 2009; Bertoglio et al. 2010)</p>	

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
Folate/folinic acid (vitamin B9)	<p>Trans-methylation pathway abnormalities (James et al. 2004; Bertoglio et al. 2010) causing oxidative stress (Villagonzalo et al. 2010)</p> <p>Neurotransmitter level abnormalities (Lam et al. 2006)</p>	<p>Correct folate/methionine metabolite profile and other indexes of oxidative stress (James et al. 2004; James et al. 2009)</p> <p>Modulate neurotransmitters (Fernstrom 2000)</p>	
Dimethylglycine (DMG)	<p>Immune system dysfunction (Goines&Van de Water 2010)</p> <p>Neurotransmitter level abnormalities (Lam et al. 2006)</p> <p>Folate/methionine pathway abnormalities (James et al. 2004; Bertoglio et al. 2010)</p> <p>Oxidative stress (Villagonzalo, et al. 2010)</p>	<p>Immunoadjuvant (Graber et al. 1981)</p> <p>Modulate neurotransmitters (Kern et al. 2001)</p> <p>Methyl donor (Kern et al. 2001)</p> <p>Antioxidant(Kern et al. 2001)</p>	General autistic behaviours
Vitamin C	<p>Neurotransmitter level abnormalities (Lam et al. 2006)</p> <p>Oxidative stress (Villagonzalo et al. 2010)</p> <p>Immune system dysfunction (Goines&Van de Water 2010)</p> <p>Deficiency (Ming et al. 2005)</p>	<p>Cofactor for neurotransmitter synthesis (Kidd 2003)</p> <p>Antioxidant (Natural Medicines Comprehensive Database 2011)</p> <p>Immune function regulation (Natural Medicines Comprehensive Database 2011)</p> <p>Prevent or treat deficiency</p>	General autistic behaviours

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
Vitamin E	Oxidative stress (Villagonzalo et al. 2010) Low erythrocyte levels (Jory & McGinnis 2007) Deficiency (Ming et al. 2005)	Antioxidant (Natural Medicines Comprehensive Database 2011) Prevent or treat deficiency	General autistic behaviours
Selenium	Oxidative stress (Villagonzalo et al. 2010)	Antioxidant (glutathione peroxidase is selenium dependent) (Thorne Research Inc. 2003)	General autistic behaviours
Calcium		Prevent or treat deficiency	Treat deficiency
Iron	Neurotransmitter level abnormalities (Lam et al. 2006) Deficiency (Latif et al. 2002)	Cofactor for neurotransmitter synthesis (Natural Medicines Comprehensive Database 2011) Optimise neural development Prevent or treat deficiency	Treat deficiency
Zinc (Zn)	Immune system dysfunction (Goines & Van de Water 2010) GI disturbance Neurotransmitter level abnormalities (Lam et al. 2006) Oxidative stress (Villagonzalo et al. 2010) Deficiency (Yorbik et al. 2004)	Immunomodulation Correct GI disturbance Modulate neurotransmitter synthesis Zn is a component of CuZnSOD Prevent or treat deficiency	

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
Probiotics	GI dysbiosis (Finegold et al. 2002; Parracho et al. 2005; Finegold et al. 2010) Heavy metal toxicity (Al-Ayadhi 2005; Fido & Al-Saad 2005)	Correct dysbiosis by promoting gut health (Parracho et al. 2010) Detoxify heavy metals (Brudnak 2002)	Normalise gut pathology
Digestive enzymes	Leaky gut (Horvath & Perman 2002)	Used in conjunction with the casein-/gluten-free diet to prevent absorption of potentially neurotoxic opioid-like peptides (Munasinghe et al. 2010)	Aid digestion/GI disturbance General autistic behaviours
Olive leaf extract	GI dysbiosis (Finegold et al. 2002; Parracho et al. 2005; Finegold et al. 2010)	Correct dysbiosis due to antimicrobial action (Markin et al. 2003)	GI abnormalities
Colostrum	Immune system dysfunction (Goines & Van de Water 2010) Lower levels of cerebrospinal fluid (CSF) insulin-like growth factor 1 (IGF-I) (Vanhala et al. 2001) Leaky gut (Horvath & Perman 2002)	Immunomodulation Rich source of IGF-I (Mero et al. 2002) GI protective (Natural Medicines Comprehensive Database 2011)	General autistic behaviours Ameliorate GI disturbance
Secretin	GI disturbance i.e. gastroesophageal reflux disease (GORD) (Patel et al. 2002) Neurotransmitter level abnormalities (Lam et	Correct GI disturbance (Patel et al. 2002) Increase GI elimination of neurotoxic substances (Patel et al. 2002) Acts as CNS neuropeptide (Levy & Hyman 2005) Increase brain neurotransmitters	Ameliorate GI disturbance General autistic behaviours

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
	al. 2006)	synthesis (Patel et al. 2002) Increase cerebral blood flow (Patel et al. 2002)	
Polyunsaturated fatty acids (PUFAs)	Functional deficiencies/imbbalances of PUFAs (Vancassel et al. 2001; Bell et al. 2004; Meguid et al. 2008) Leaky gut (Horvath&Perman 2002)	Optimise neural development (Freeman et al. 2006) Prevent or treat deficiency (Meguid, Atta et al. 2008; Bent et al. 2010) Reduce GI inflammation (Garvey 2002)	Cognition Attention/hyperactivity GI abnormalities
Melatonin	Tryptophan deficiency (melatonin precursor) (D'Eufemia et al. 1995; Arnold et al. 2003) Lower excretion rate of 6-sulphatoxymelatonin (melatonin metabolite) (Tordjman et al. 2005) Oxidative stress (Villagonzalo et al. 2010)	Normalise melatonin levels to reduce sleep latency Antioxidant (Natural Medicines Comprehensive Database 2011)	Improve sleep quality
Allithiamine/ thiamine tetrahydrofuryl disulphide (TTFD)	Heavy metal toxicity (Al-Ayadhi 2005; Fido & Al-Saad 2005) Impaired sulphation capacity (Waring&Klovrza 2000) Reduced excretion of cyanide i.e. lower urinary thiocyanate (Waring&Klovrza 2000)	Chelate and reduce heavy metal levels (Lonsdale 2004) Enhance sulphation capacity by acting as a sulphate donor (Waring&Klovrza 2000) Enhance excretion of neurotoxic cyanide (Lonsdale 2004)	General autistic behaviours
Dimercaptosuccinic acid (DMSA)	Heavy metal toxicity (Al-Ayadhi 2005; Fido & Al-Saad 2005)	Chelate and reduce heavy metal levels (Lonsdale 2004; Adams et al. 2009)	General autistic behaviours

CAM product used in autism	Abnormality theorised/reported to occur in autism	Rationale for use	Specific symptom/behaviour targeted
Metallothionein promotion	Elevated blood copper-to-zinc ratios (Faber et al. 2009)	Regulate levels of redox-active metals (Copper (Cu) and Zn) (Faber et al. 2009) Defense against toxic heavy metals (Faber et al. 2009)	General autistic behaviours
Glutathione	Abnormal trans-sulphuration pathway leading to low GSH:GSSG (James et al. 2004; James et al. 2006), an index of oxidative stress (Villagonzalo et al. 2010)	Antioxidant (Thorne Research Inc. 2001) Augments chelation therapy (Thorne Research Inc. 2001) Regulates metallothionein expression (Thorne Research Inc. 2001)	General autistic behaviours
Glutamine	Abnormal glutamine levels (Shinohe et al. 2006)	Enhance immunity (Natural Medicines Comprehensive Database 2011) Is a pre-cursor to glutathione (see above) GI protective (van der Hulst&van Kreel 1993)	General autistic behaviours GI abnormalities

Table 2. CAM products used in autism, theoretical or proven abnormality in autism, rationale for use and symptom/behaviour targeted

5. Conclusion

Available evidence for the theoretical or proven rationale of a range of CAM products has been compiled to give researchers and health professionals insight into why such agents are recommended and implemented in autism. This information forms the basis for the second part of this 2-part review which follows examining the efficacy and safety of a range of CAM products used in autism.

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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