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Autism spectrum disorder: A review of the current understanding of pathophysiology and complementary therapies in children

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Abstract: Autism is a complex condition which affects speech, language, neurodevelopment, sensory perception and social interaction. Until recently the pathophysiology of this condition has been poorly understood. Immunological and neurological research in autistic patients has improved the understanding of autism greatly. It is important that this research filters through to clinical practice, so that appropriate therapies may be employed. Autism requires a multidisciplinary approach to maximise the potential of patients affected by it. As such, it is important that different models of care support each other and do not place undue stress on the patient. Natural therapies can play a key role in supporting the outcomes of other therapies such as psychology, occupational therapy and speech therapy, and by doing so, improve lifelong outcomes.

Diagnosis

Autism Spectrum Disorder (ASD) is a developmental disorder which affects language development, social interaction and communication and involves restrictive and repetitive areas of interest and behaviours (London 2007). It is a spectrum of disorders which includes Asperger's Disorder, Disintegrative Disorder, Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) and Atypical Autism (Meletis 2007). Diagnosis involves a multidisciplinary team, which includes assessment of verbal and nonverbal communication, adaptive behaviours, atypical behaviours, fine and gross motor skills and cognitive status (Samtani 2011). The ways in which this presents in children vary significantly.

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) has recently replaced DSM-IV. Autism Spectrum Disorder is now an umbrella diagnosis, as opposed to being differentiated into different categories. The main criticism of the previous diagnostic criteria (DSM-IV) is inconsistency of diagnosis (Kaufmann 2012). Previously Asperger's Disorder (AD) was differentiated from High Functioning Autism by the lack of language delay (Entiticotti 2010). There is however no pathophysiological differentiation between these two categories (Kaufmann 2012). The new diagnostic schedule attempts to simplify the diagnosis and encourage the diagnosing physician to include a description of the key areas of difficulty for each individual, thus giving clarity to individual variation within the spectrum (Table 1). This description would include: details regarding the severity of ASD symptoms; verbal abilities; the pattern of onset; clinical progression; etiologic factors; cognitive abilities (IQ); and associated conditions or co-morbidities. It is hoped that the new diagnostic criteria will simplify access to services for children with ASD and that the diagnostic report will give more specific information to other therapists involved in the co-management of a child with ASD (Kaufmann 2012).

Table 1: Current diagnostic criteria for autism spectrum disorder

Kaufmann WE. DSM-V: The New Diagnostic Criteria for Autism Spectrum Disorders. Department of Neurology Boston Children's Hospital, Harvard Medical School. http://autismconsortium.org/symposium-files/WalterKaufmannAC2012Symposium.pdf

Currently, or by history, must meet criteria A, B, C, and D
A. Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following: 1. Deficits in social-emotional reciprocity 2. Deficits in nonverbal communicative behaviours used for social interaction 3. Deficits in developing and maintaining relationships
B. Restricted, repetitive patterns of behaviour, interests, or activities as manifested by at least two of the following: 1. Stereotyped or repetitive speech, motor movements, or use of objects 2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behaviour, or excessive resistance to change 3. Highly restricted, fixated interests that are abnormal in intensity or focus 4. Hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment
C. Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities)
D. Symptoms together limit and impair everyday functioning.

Incidence

The diagnosis of ASD has rapidly increased over the last 20 years. In the early 1990s prevalence of ASD in western countries was estimated at 1 in 1000. In 2002 rates of autism have been reported as 1 in 150 (6.6 in 1000). Other authors report incidence at 1.5-2% (i.e. 15-20 in 1000). Rates vary geographically and are reported differently. For example, there has been lower prevalence reported in Alabama with 3.3 per 1000 8-year olds diagnosed with ASD, compared to New Jersey with 10.6 per 1000 8-year olds. Furthermore, rates of autism seem to be rising faster than can be explained by improved diagnosis (London 2007).

Why are the rates of autism increasing?

Current research suggests that prenatal factors significantly influence the incidence of ASD. Prenatal exposure to rubella or cytomegalovirus greatly increases the risk for autism (Patterson 2009). It has been estimated that if viral (influenza, Herpes simplex virus, rubella), bacterial (urinary tract) and parasitic (toxoplasma) infections could be prevented in pregnant women, >30% of schizophrenia cases could be prevented (Patterson 2011). This research is relevant when looking at prenatal ASD risk, in that schizophrenic patients show similar cytokine dysregularity and that this dysregularity remains in the offspring through childhood into adulthood (Patterson 2011). Increased rates of positive reactivity for several serum antibodies to specific CNS proteins have been observed in children with autism, specifically affecting the basal ganglia, the frontal lobe, the cingulate gyrus and the cerebellum (Zimmerman 2007). Interleukin-6 (IL-6) has been implicated in pathogenic changes to brain development in vivo (Smith 2007). IL-6 interferes with transcription pathways that regulate neurogenesis and gliogenesis (Smith 2007). Additionally other studies, both animal and human, have demonstrated the production of maternal antibodies which interfere with prenatal brain development (Zimmerman 2007). These immunological patterns in-utero may be responsible for altered serum reactivity and other immune system dysregularity observed in children and adults with ASD (Zimmerman 2007).

Advanced maternal and paternal age has also been associated with increased incidence of ASD (Croen 2007). While studies looking at the influence of maternal and paternal age are not consistent, a 2009 meta-analysis found that each independently increased the incidence of ASD (Gardener 2009). One study suggested that, if parental age is causal, 4-13% of ASD cases could be attributed to parental age being >35 years (Croen 2007).

While many independent prenatal factors are associated with increased incidence of ASD, the current understanding is that no single factor is causative. Genetics may also have a big part to play. Parents with one ASD child have a 27% chance of having subsequent children with ASD (Tomeny 2012). The current thinking is that genetics create a predisposition, and prenatal factors influence the likely expression of those genetics and the severity of impact on the child. In a clinical setting, these trends highlight

Table 2: Maternal factors associated with increased ASD incidence

Maternal history	Maternal Tertiary education	
	Previous foetal loss	Gardener 2009
	Atopic disease (40% of mothers of children with ASD have some kind of allergy)	Mostafaa 2008
	Vitamin D deficiency	Nagwa 2010, Fernell 2010
Prenatal factors	Twofold increase in incidence of autism in children whose mothers used an SSRI (Selective Serotonin Reuptake Inhibitor) antidepressant in the year prior to delivery	Croen 2007
Peri-natal factors	Induction of labour	Juul-Dam 2001
	Labour <3 hours	Juul-Dam 2001
	Prolonged labour >20 hours	Gardener 2009
	Pre-eclampsia	Gardener 2009
	Maternal hypertension	Gardener 2009
	Oxygen required at birth	Gardener 2009
	Rhesus incompatibility	Gardener 2009
	Almost fourfold increase in incidence with SSRI antidepressant use in first trimester	Croen 2007
Birth order	1st born and 4th or subsequent children	Tomeny 2012
Infant feeding	Absence of breastfeeding	Al-Farsi 2012
	Reduced period of exclusive breastfeeding	Al-Farsi 2012
	Late initiation of breastfeeding (no colostrum)	Al-Farsi 2012
	Early weaning	Al-Farsi 2012

the importance of preconception care, particularly as the average age of childbearing increases and more so in couples with a family history of ASD or atopy.

Pathophysiology

Specific physiological and biochemical differences have been observed in people with ASD that are pertinent to the therapist's understanding of autism and have bearing on clinical treatments and outcomes.

Hyperserotonemia has been observed in 25-40% of children and adolescents with autism (Aldred 2003, Kidd 2003). Dopaminergic imbalances are also common, with likely dopamine insufficiency in CNS (Kidd 2003). Imbalances in serotonin and dopamine will influence prevalence of anxiety and depression in people with ASD, and should be considered during the assessment process. Reduced γ-Aminobutyric Acid (GABA) proteins have also been observed in people with autism, as well as down regulation of GABA receptors (Fatemi 2010, Fatemi 2009). GABA is involved with inhibitory actions in the brain.

Neurophysiology

Significant differences in brain structure and functionality have been observed via magnetic resonance imaging and autopsy in children with autism as detailed in Table 3.

To put it simply, the brain is structured differently in individuals with autism. While ASD affects many systems within the body it is also a neurological disorder. Many of the challenges that people with autism face, such as social difficulties, language difficulties, sensory issues and processing speed, directly relate to these differences in the way the brain is structured and how it communicates with other areas of the brain. Altered balance of local and global connectivity in the autistic brain may lead to development of prodigious skills coexisting with impaired executive function and social cognition (Takahata 2008). This may present as enhanced memory skills or exceptional skills in fixed areas of interest. Global connectivity between prefrontal cortex and other areas of the brain may explain cognitive impairments, impulsivity and restriction of interests (Takahata 2008). Reduced neuron recruitment could explain slower processing speed and transition difficulties (Agam 2010, Kenet 2012). This may also explain exam difficulties where autistic students focus intensely on early exam questions at the expense of the rest of the exam.

Oxidative stress and inflammation

People with ASD also exhibit raised biochemical markers for lipid oxidation and inflammation. Lipid peroxides are significantly raised, as are urinary isoprostanes. Lipofuscin in the cortical brain is elevated, which is a marker of oxidative tissue damage. Lower levels of antioxidants (both enzymes and nutrients) have been observed in autistic patients. This includes lower levels of total plasma glutathione, plasma vitamins C, E, A, and red-cell selenium (McGinnis 2004).

Higher levels of inflammation and free radical production have been observed in autistic patients, both in the gastrointestinal system and the brain. Inflammation in the gastrointestinal system raises cytokine production systemically, which in turn promotes a hyper-permeable blood-brain-barrier, apoptosis, neurodegeneration and demyelination (McGinnis 2004).

Allergies and gastrointestinal hyper-permeability

Increased gastrointestinal permeability is also common in people with ASD. Food allergy and intolerance is common and may be the underlying cause of gastrointestinal hyperpermeability or may be consequential. The C4B null allele is present in 42% children with autism, which predisposes for autoimmune and allergic development (Mostafaa 2008). Lactase deficiency may be present in up to 58% of children with ASD ≤5 years old (Kushak 2011). Furthermore, a 2008 study found 52% of children with autism had some kind of allergic disease, and that children with gastrointestinal symptoms and ASD had an 88% chance of allergic

Table 3: Neurological and functional differences observed in children with ASD

Structural differences	Decreased cerebellum size	Wagner 2006
	Altered number of Purkinje cells	Wagner 2006
	Altered hippocampus size and cell number	Wagner 2006
	Overall brain size is greater, with increased neurons in cerebral cortex	Vaccarino 2009
Functional differences	Decreased activity in temporal lobe	Wagner 2006
	Basal ganglia show structural changes and functional impairment	Wagner 2006
	Reduced connectivity between the cortical ocular motor control network	Kenet 2012
	Reduced neuron recruitment to prepare for task difficulty	Kenet 2012
Neurotransmitter differences	Changes to dopaminergic and serotonergic activity in the striatum	Wagner 2006
	Up to 40% have raised serotonin levels	Kid 2003
	Dopaminergic imbalances are common, with likely dopamine insufficiency in CNS.	Kid 2003

disease (Mostafaa 2008). Understandably, malabsorption syndromes are common, particularly when there is an underlying food allergy/intolerance that has not yet been identified or effectively eliminated. Abdominal pain, discomfort, bloating, diarrhoea, anorexia and other signs of gastrointestinal upset should be assessed. In autistic children who are nonverbal this may be difficult to assess. Additionally they may have had these symptoms for so long that they do not understand that this is not normal. Other manifestations of atopy such as hay fever, asthma, eczema and allergic rhinitis should also be assessed.

Family and social context

In treating a child with ASD one must also consider the family context. Recent studies have examined the implications of ASD on other siblings within the family. Neurotypical children with an older sibling with ASD are more likely to exhibit higher levels of behavioural difficulties or language delay, and other subclinical characteristics of ASD (Tomeny 2012, Constantino 2010). Stress levels within the home in these families can be extreme and in such situations the role of adaptogens should not be underestimated. Various television programs have popularised a very bleak picture for families of autistic children, suggesting divorce rates of 80- 85% (Winfrey 2007, Lofholm 2008). While these figures are alarming, they are not consistent with recent studies (Higgins 2005, Hartley 2011, Mailick-Seltzer 2011, Naseef 2012, Baeza-Velasco 2013).

A study conducted at the University of Wisconsin in 2010 compared data collected from 406 adolescents and adults living with ASD to the national standard (Hartley 2011). This study found that 23.5% of parents having a child on the spectrum separated, compared to the national average 13.8% (Hartley 2011). Similarly a 2013 study of 119 families in Victoria, Australia reported a 25.2% separation rate in parents with an ASD child (Baeza-Velasco 2013). Furthermore the Wisconsin study found that whilst in families without a child with a disability the divorce rate tends to decline once the child is over 8 years old, it remains high in couples with an autistic child (Hartley 2011). The authors speculate that while family stress levels are highest in most families while a child is quite young, these pressures become less as the child becomes more independent. In families with an ASD diagnosis this reduction in stress levels does not occur.

Many people with ASD continue to need support well into adulthood and as such family stress levels may remain high for a much longer period of time. A 2012 study stated that seventy-five percent of people with autism will require lifelong educational and social support (Mefford 2012). Consequently, parents of children with ASD experience worry and anxiety for their offspring for much longer periods of their lives and lack the surety that their child will be able to live a fulfilling and independent life. Providing support for parents using stress management strategies thus becomes part of the natural therapist's role in the treatment of a child with autism.

Barriers to diagnosis

Reluctance to "label" often may become a stressor that divides parents and is in itself a limitation to starting effective treatment. Possibly with the exception of regressive cases of autism, signs are usually present very early in a child's life (Teirney 2004, Matson 2012). Eighty percent of parents have reported some concern about a child's development by 18 months old and diagnosis usually occurs between 2 ½ - 4 ½ years old (Mundkur 2005). Early intervention strategies, including speech and occupational therapy, utilise the increased neuroplasticity that is present in very young children. Neuroplasticity, the ability of the brain to develop new neuron connections in response to stimuli or experience, is greatest for visual stimuli before the age of seven years, and greatest for language acquisition before age six years (Mundkur 2005). Current research suggests that early intervention helps to minimise the severity of lifelong symptoms (Teirney 2004, Matson 2012). The importance of the role of the health professional in facilitating early diagnosis cannot be overstated. Dismissing a parent's concern may be harmful in that it delays assessment of the child and subsequently delays access to support and therapies. Parents and teachers are the best placed people to identify problems that a child may be having. It is imperative that their concerns be taken seriously so as not to lose a critical therapeutic window for neurodevelopment.

Speech delay and language difficulties

Where speech delay is absent, people with ASD are likely to have disorganised or very unusual language, or may speak monologues in specific areas of interest (Woodbury-smith 2009). Echolalia is often used as means to communicate and is typically more advanced in children without a language delay. Echolalia is most simply described as a cut and paste strategy for learning language. Rather than learning how to put individual words together and formulate a response to a question, the child learns phrases or sets of words that can be memorised and effectively used to respond to particular questions. These phrases or sets of words are often learnt from dialogue on television or from peers or parents. These phrases may make learnt responses unusual. They may have limited or repetitive responses and may not answer at all if the question is one to which they do not know how to respond. A speech stutter is also common in people with ASD and is more likely when anxiety is also a problem (Davis 2011).

Language comprehension is also limited in that language processing is very literal (Law 1995). This is often perceived as a lack of sense of humour in the ASD child, as they have difficulty differentiating sarcasm and untruths from normal conversation. They often have difficulty with making and keeping eye-contact with other people and have marked difficulty observing and

interpreting differences in body language and facial expressions. Socially this makes them vulnerable to being the butt of jokes or school yard pranks and creates a certain gullibility that if not careful, can be exploited. Colloquial phrases also create difficulty, because they do not make literal sense. Children are told "pull your socks up," or "jump into bed," and may interpret this literally. For children with ASD this creates further frustration and confusion, particularly if they are chastised for doing literally what they are told.

Processing auditory language can be particularly difficult (Law 1995). Children on the autism spectrum are often visual learners. In a classroom setting this creates difficulty if the teacher relies heavily on verbal instruction. These children benefit greatly from visual teaching methods. Predicting sequential activities throughout the day can also be particularly difficult for people with ASD, even if the routine is well established. A simple but effective strategy for this is the use of a *visual schedule.* A visual schedule can be a list, in pictures or words, that lets the child know what to expect, and greatly reduces anticipatory anxiety (Curtis 2010).

Co-morbidities

Co-morbidities are common in children with ASD and may also need specialist attention (Table 4) (Matson 2009). It is important to consider the relevance of these co-morbidities, what they tell us about the individual challenges for the patient and the impacts they have on the patient and their family. Sleep disorders are common. In ASD patients there has been observed a genetic difficulty in melatonin synthesis (Golink 2010). This presents as difficulty getting to sleep and staying asleep, with obvious secondary impacts on daytime alertness, mental function and coping skills. Depression and anxiety are also common, which is likely explained by alterations in levels and responsiveness to serotonin and dopamine (Kidd 2003). Obsessive-compulsive disorder may also be co-diagnosed, though it is arguable that being obsessive about fixed areas of interest is part of being autistic. Lack of ability to maintain attention, or symptoms of hyperactivity (as in ADHD) are also within the scope of ASD, and suggest that there are sensory processing issues that need further addressing.

Sensory Processing Disorder (SPD)

Sensory Processing Disorder (SPD) is a common feature of ASD. SPD refers to the process of receiving sensory messages by the nervous system and the conversion of those messages into responses (Miller 2006). In people with SPD the brain lacks the ability to filter out all the background sensations. In SPD one or more of the senses may be hyper-acute and the brain lacks the ability to prioritise some sensory information over others (Miller 2006). This affects the way in they respond to others, in that verbal instructions compete with a myriad of other sensory information the child is trying to process (Miller 2006, Shandley 2012, Curtis 2010). The lack of filtering of sensory information, combined with altered connectivity within the brain, slows processing time and results in delayed or absent responses from the child.

Children on the spectrum express SPD in a few different ways. Some are described as exhibiting sensory-seeking behaviour, sensory under-responsivity, and sensory overload or defensiveness. When a child exhibits sensory-seeking behaviour, they seek activities that exhilarate the senses in order to control sensory input and maintain a sense of equilibrium, for example running, jumping or spinning (Curtis 2010).

Children who exhibit sensory under-responsivity tend more to withdraw, or seek quiet, sedentary games, or have reclusive interests. These children may also be unresponsive to their own physical needs (eg: toilet, hunger, food left on face, runny nose). They may be slow or unmotivated to learn to dress themselves, slow with toilet training, unresponsive to changes in temperature and unaware of what is going on around them. Children

Table 4: Common co-morbidities in children with ASD

Condition	Prevalence	Reference
Anxiety	< 84%	Davis 2011, White 2009
Sleep disorders	75%	Teirney 2004
Allergic manifestations (asthma, atopic dermatitis and/or allergic rhinitis)	52%	Mostafaa 2008
Depression	< 50%	Teirney 2004
ADHD	45% of children with ASD meet the diagnostic criteria for ADHD	Skokauskas 2012
Symptoms of epilepsy	33%	Teirney 2004
Obsessive-compulsive disorder	10%	Gjevik 2010
Tourette's syndrome	6%	Teirney 2004
Fragile X Syndrome	1%	Teirney 2004

with SPD may also exhibit characteristics of both sensory under-responsivity and sensory seeking at different times (Miller 2006).

Sensory overload/defensiveness occurs when the individual who is unable to filter out background sensation (smell, sight, sound, touch, taste, proprioception) becomes overwhelmed (Miller 2006, Shandley 2012). Sensory overload creates enormous anxiety for the individual and the person will often try to "escape" a challenging/overwhelming situation (Miller 2006, Curtis 2010). A person may use appropriate or inappropriate means to remove themselves or withdraw from a situation. When anxiety levels are high, fight or flight mechanisms are used and the ability of the individual to think clearly and make appropriate decisions is diminished (Curtis 2010). Level of skill, or ability to make situation appropriate choices reduces in proportion to the increase in level of anxiety being experienced (Curtis 2010). Disruptive or challenging behaviours are often used by children with SPD in situations where they feel overwhelmed because they lack the skills to figure out how to withdraw from a challenging situation in a way that is socially appropriate. The unfortunate outcome of these situations is often discipline, punishment, further alienation and lowered self-esteem (Curtis 2010).

Occupational therapy may be used to help the child learn appropriate means to remove themselves from a situation when feeling overwhelmed. However it is equally important that carers and teachers are aware of the child's individual triggers. Observation in the classroom by the occupational therapist helps with this process, followed by negotiation involving teacher, parent, therapist and child to make the class-room a less overwhelming environment and more conducive to the child's learning (Curtis 2010). Fundamental to this process are agreed-upon means by which the child can withdraw to a quiet space or engage in physical activity when needed.

Mortality

Mortality rates have been found to be at least double the rate of the neurotypical population, with one study suggesting it is 5.6 times the expected rate (Gillberg 2010, Mouridsen 2008). This rate was higher in females than males (Gillberg 2010). Seizures are a large contributor to mortality rates. Impulsivity and compulsivity may also be significant contributing factors. Parents of children on the spectrum are often hyper-vigilant with their children because they are aware that their child is compulsive and additionally may not be able to predict cause and effect.

Multidisciplinary management of autism

Autism requires a multidisciplinary approach and will need good communication between therapists. For practicality, parents will often have to prioritise some therapies over others, depending on the child's specific needs at the time (Table 5).

Evidence-based natural therapies and lifestyle recommendations

Many strategies the natural therapist may employ will be based on assessing the individual needs of the patient alongside an understanding of what we now know to be the underlying pathophysiology of autism. While much of this research is preliminary, the following treatments have an evidence base.

Gluten free casein free diet (GFCF)

A controlled, single-blind, Scandinavian trial in 2010 found improvements in core autistic behaviours using a gluten-free casein-free diet (GFCF diet) over an 8-12 month period (Whitely 2010). This study found a higher dropout rate with adolescent patients. Improvements were observed in communication, social functioning, attention, concentration and hyperactivity. Improvements in social interactiveness, and stereotyped and repetitive behaviours were observed after 24 months (Whiteley 2010). A pilot study in 2012 noted that whilst 100% of parents with a child on a GFCF diet noticed improvements in behaviour and gastrointestinal symptoms, these results were not clinically verifiable (Harris 2012). It is important

Table 5: Medical and allied health professionals involved in the care of children with ASD

Therapist	Role
Paediatrician	Initial diagnosis; access to funding/rebates; Co-ordinate and prioritise therapies.
Speech therapist	Assist with language delays, stutter, disorganised speech, and orosensory motor issues
Occupational therapist	Address sensory overload/defensiveness issues; negotiates with school to adapt classroom and develop routines to accommodate child's needs; Facilitates social development; may help with fine motor skills.
Physiotherapist	Assists with developing gross motor skills.
Psychologist	Assist with developing social skills as well as specific issues such as sibling rivalry, bullying, victimising, exclusion, and poor self-esteem.
Psychiatrist	More often involved with the older child or adult. Psychotropic medication use has been reported as 45% of children and adolescents with autism (Golink 2010).

to note that this study used a reduced gluten and casein diet (8.7 gluten or casein foods per week, compared to 53 for the control) rather than a strict GFDF diet.

These results were not seen in a 2011 study over a three month period (Johnson 2011). Possible limiting factors were the difficulty of not being able to blind parents to the treatment regime and that the control used was a healthy low-sugar diet.

Fundamental to the success or failure of a gluten-free diet is the capacity to provide appropriate food substitutes for gluten-containing foods. Other issues that may limit success may include the willingness of parents to adapt to a new diet and the willingness of the child to try new foods. Other factors such as oro-sensory issues, other food allergies or intolerances and a history of previous attempts at dietary exclusions may also be a limitation.

To assess these issues a 2008 pilot study focused on developing an acceptable protocol and method for assessing a GFCF diet (Adams 2008). The authors of this study attempted to develop a range of foods that children would accept and that were transportable, easy to prepare and nutritionally suitable. Given the habitual tendencies and food fussiness inherent in many children with ASD, the trial aimed to assess the willingness of children to try new foods. Recruitment consisted of 52 children aged 3-6 years. The study found that 95% of the children tried some of the new foods and only three families dropped out of the study due to food refusal. Parents commented that there needed be a savoury staple (e.g. bread) included. The authors concluded that families of these children were very motivated to participate in dietary research specific to ASD and that finding acceptable food substitutes is critical for this kind of study to be of clinical significance (Adams 2008).

Vitamin C

A 30 week double-blind placebo-controlled trial showed decreased symptom severity in children with ASD. A dose of 8g/70kg/day of ascorbic acid resulted in significant improvement in total interaction scores and sensory motor scores. The mechanism of action may be via the dopamine-potentiating effect of vitamin C demonstrated in earlier studies, in addition to its antioxidant role (Dolske 1993, Shin 1988).

Multivitamin-mineral supplement

A small pilot study of 20 children aged 3-8 years with ASD investigated the effects of a "moderate" multivitamin supplement. The study reported significant improvements in gastrointestinal symptoms and sleep (Adams 2004).

Vitamin B6

Vitamin B6 is a co-factor for 113 enzymes, including neurotransmitters serotonin, GABA and the catecholamines (Adams 2006). Supplementation of vitamin B6 in ASD has been extensively studied. Of 22 studies conducted, 21 show improvement in ASD (Bihari 2006). Pyridoxal kinase has been demonstrated to have very low activity in children with autism (Adams 2006). Low activity of pyridoxal kinase results in low levels of pyridoxal-5-phosphate (PLP) and high plasma levels of total B6, due to impaired conversion of pyridoxine and pyridoxal to PLP (Adams 2006). Plasma levels of total B6 have been observed to be 75% higher in autistic children (Meletis 2007).

High dose B6 may improve function of pyridoxal kinase, which may explain improvements in mental and physical function in ASD (Adams 2006). Doses used in studies ranged 100-600mg/day (Pfeifferi 1995).

Magnesium and B6

Red-blood-cell levels of magnesium have been observed to be lower in children with ASD (Meletis 2007). In 2006 a study was conducted using magnesium (6mg/kg/d) and B6 (0.6mg/kg/d) in autistic children. Seventy percent of children showed significant improvement (Meletis 2007). Additionally there is positive research to support the use magnesium in the treatment of anxiety (Lakhan 2010). It is therefore well worth considering in patients with ASD.

Vitamin B12 and Folic Acid

People with ASD have reduced methylation of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), and Glutathione (GSH) to its oxidised form Glutathione disuphide (GSSG). These ratios (SAM:SAH) and (GSH:GSSG) are indicative of reduced methylation capacity and increased oxidative stress. A 2009 study used 75mcg/kg injected methylcobalamine with 400mg folinic acid daily for 3 months. This resulted in improved serum ratios but not normalised to levels of neurotypical people. Despite this, significant improvements in behavioural symptoms were observed. This finding is consistent with other studies (James 2009, Bertoglio 2010).

Carnosine

An eight week trial (n=31) using 800mg L-carnosine showed significant improvement in behaviour, communication and social ASD traits (Chez 2002). Mild improvements in other ASD traits were also observed. Carnosine is an antioxidant, has antiglycating activity and binds heavy metals (Meletis 2007). Carnosine also appears to enhance frontal lobe function, and have a neuroprotective effect (Chez 2002).

Omega 3 fats

The need for adequate levels of EPA and DHA is seen especially during pregnancy. However, strategies that utilise neuroplasticity could also benefit from the fluidity provided by these nutrients. Neuroplasticity requires cell fluidity to develop new axons, dendritic extensions and synapses, and DHA is the most fluid component of cell membranes (Kidd 2007). Many studies have been conducted to assess the clinical application of omega 3 fats in the treatment of autism.

In 2007 a small 6-week pilot study (DBPC n=12) was conducted in boys with ASD aged 5-17 years (Amminger 2007). Test subjects were given 7g fish oil (FO) in capsules (840mg EPA, 700 mg DHA, 7mg vitamin E). Placebo consisted of 1g Coconut oil, 1mg vitamin E, 1mg FO to mimic fishy taste. The results of this study demonstrated a mild improvement in inappropriate speech (39%), and larger improvements with stereotypy (72%) and hyperactivity (71%) (Amminger 2007).

In 2009 a systematic review was conducted in which only 6 out of the retrieved 143 studies satisfied the inclusion criteria and were included (Bent 2009). The authors reported that while there is broad use of FO supplementation in ASD, so far there is little quality evidence to support it (Bent 2009). Similarly a 2011 Cochrane review concluded insufficient statistical evidence (James 2011). Inherent difficulties in adequately assessing evidence for the use of omega 3 fats in ASD include the inability to easily blind a benign placebo, the use of inadequate doses, and recruitment of small sample sizes.

Exercise

A 2012 meta-analysis concluded that exercise significantly improves motor skills, social skills and communication skills (Sowa 2012). Most studies consisted of small groups and lacked a control group. Most studies achieved a positive result in the targeted area. Exercise regimes included cycling, aerobic exercise, swimming and horse riding (Table 6).

Acupuncture

A 2011 Cochrane review included 10 trials that involved 390 children with ASD. Age ranged from 3-18 years and the treatment duration ranged from four weeks to nine months (Cheuk 2011). The authors concluded that there is no statistical evidence to support the use of acupuncture in children with ASD. However, 2 trials showed improvement in secondary outcomes of communication, linguistic ability, cognitive function and global functioning. A further 6 trials showed improvement in secondary outcomes of cognitive function and global functioning. A positive result was also found in secondary outcomes in 2 acupressure trials, which showed improvement in communication and linguistic ability, cognitive function and global functioning (Cheuk 2011).

Interpretation of reviews is limited by target outcomes, the quality of original studies and the qualitative nature of assessing core ASD features. While these studies did not show improvement in target areas, they did demonstrate improvement in other areas of difficulty in ASD and as such may be clinically relevant.

Animal assisted therapy

Animals may play a role in improving the quality of life of children and adults with autism. In severe cases this may be as a service dog (Adams 2010). In most cases, however, this is more likely to be the household pet. The child may be given set tasks involved with the care of the animal, so that they develop a sense of responsibility. Having a pet helps a child develop empathy, consideration of others' feelings and self-confidence (Adams 2010, Law 1995). The animal may also be a source of comfort and unconditional love for the child. Prosocial behaviours such as offering to share and offering comfort, has also been observed in autistic children with the introduction of a pet (Grandgeorge 2012). Care must be taken when making this recommendation. People on the spectrum often are atopic, may have specific phobias, and their families are often extraordinarily busy. It is important to consider the type of pet and the potential negative and positive outcomes for the child and their family within the scope of this recommendation.

Conclusion

Autism is a very complex condition that requires a multidisciplinary approach to maximise the child's potential. It is important to have a thorough understanding of the pathophysiology underlying this complex disorder in order to understand the core characteristics present in autistic children. Research developments have improved the understanding of the aetiology and pathophysiology of autism spectrum disorders, which can now be considered

Table 6: Effect of exercise on ASD symptoms

Exercise	Study size	Outcome	Reference
Cycling	n=3	Improvements in terms of self-efficacy, group participation and physical endurance.	Todd 2010
Aerobic exercise	n=5	Reduction in self-stimulatory behaviour. Participants performed better at set tasks, both in terms of accuracy and amount of tasks completed.	Rosenthal-Malek 1997
Swimming	n=16	Increased water confidence and competence. Decreased antisocial behaviour, but not increased social competence. Valuable opportunity for peer support, socialising and verbal instruction practice.	Pan 2010
Horse riding	n=29	Improved self-concept.	Cawley 1994
Horse riding	n=19	Improved sensory receptivity and social motivation. Less sedentary behaviours and distractibility.	Bass 2009

to be genetic, neurological, immunological, pro-inflammatory and pro-oxidant. While there is preliminary research of some natural therapies and dietary approaches, there is great scope for further research as to the role of complementary therapies in the treatment of autism. These therapies range from lifestyle and exercise regimes, to nutritional supplementation and dietary modification. Further research as to how complementary therapies might be used to maximise the potential of children with autism and support other modalities is therefore warranted.

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include direct antibacterial activity, indirect antibacterial activity such as inhibition of host epithelia and group A streptococci, improved phagocytosis, improved oxidative burst and intracellular killing by human peripheral blood phagocytes, release of tumour necrosis factor and nitric oxides and a number of other activities. Previous meta-analysis of clinical trials with EPs 7630 in acute bronchitis indicate superior efficacy in symptom resolution when compared with placebo. The current study was the first to extend this research to COPD patients and examine whether EPs 7630 administration could reduce time to first exacerbation and reduce exacerbation frequency as an adjunctive therapy.

The randomised, double-blind, placebo-controlled trial involved 200 patients with chronic bronchitis from 18 centres across the Ukraine. Over a 24-week treatment period the participants took either EPs 7630 or matched placebo as an add-in treatment to their existing regime. Dosing of the medication was 3 x 30 drops daily. Over the course of the study participants documented on a daily basis: chronic bronchitis symptoms, health status and consumption of all medications. In addition they undertook seven regular visits to the treatment centre and intermediary visits in case of an exacerbation. Baseline assessments included: physical examinations, laboratory tests, chest X-ray, bronchitis symptom score of cough, sputum and sternal chest pain, and spirometry tests to determine FEV1 and FVC before and after ipratropium-bromide/fenoterol (NB. this was used in the place of salbutamol in reversibility testing as salbutamol was not available in the Ukraine at this time).

The primary outcome measure of the study was time to first COPD exacerbation (reported or unreported, as assessed by increases in medication to self-manage COPD symptomatology). Secondary outcome measures were: number and duration of exacerbations, health status, patient satisfaction with treatment and duration of inability to work.

Overall median time to exacerbation was 57 days in the EPs 7630 group and 43 days in the placebo group. The probability of remaining free of COPD exacerbation was significantly higher in the active treatment group. For EPs 7630 patients the median duration of exacerbation was also a day shorter (11 v 12 days) and far fewer required antibiotic treatment (37.8% of patients compared with 73.3% of patients on placebo). Patient satisfaction with the intervention was significantly higher in the active treatment group after 24 weeks and the mean number of days off work was also significantly lower in this group. However the rates of mild gastrointestinal disturbance were higher in the Pelargonium treatment arm.

The results of this study indicate that EPs 7630 (and by extrapolation, similar extracts of Pelargonium) may be of use as an additional treatment to prevent and treat exacerbations in patients with moderate to severe chronic bronchitis.

Anti-aging effects of *Withania Somnifera*

Kumar R, Gupta K, Saharia K, Pradhan D, Subramaniam J. 2103. *Withania somnifera* root extract extends lifespan of *Caenorhabditis elegans*. *Ann of Neurosc* DOI:0.5214/ans.0972.7531.200106.

Withania Somnifera (WS) is a herb most Western herbalists are familiar with. It has a long history of use in Ayurvedic medicine, in which it is claimed to have longevity-enhancing effects. However this has never been proven.

Researchers from the Indian Institute of Technology in Kanpur set out to evaluate whether an extract of *Withania Somnifera* root could indeed have anti-ageing effects. In the past the major challenge with studies assessing lifespan was the long-time requirement in mammalian models (even murine models). However recent studies now use the model organism *Caenorhabditis elegans,* an organism with fundamental mechanisms and systems similar to the mammalian system. This organism has a naturally short lifespan but the mechanisms which increase its longevity, identified in previous studies of C. elegans, are remarkably similar to those reported in mice, flies and humans.

They found that when *C. elegans* worms were treated with WS extracts, they demonstrated a 21.4% lifespan extension in comparison to control. This research must be taken with a grain of salt as it was funded by the company that produced the extract and it is only initial data. However it opens interesting avenues for further investigation. Herbalists may wish to consider WS as part of a healthy-ageing strategy for those clients who wish to optimise their health as they age.

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