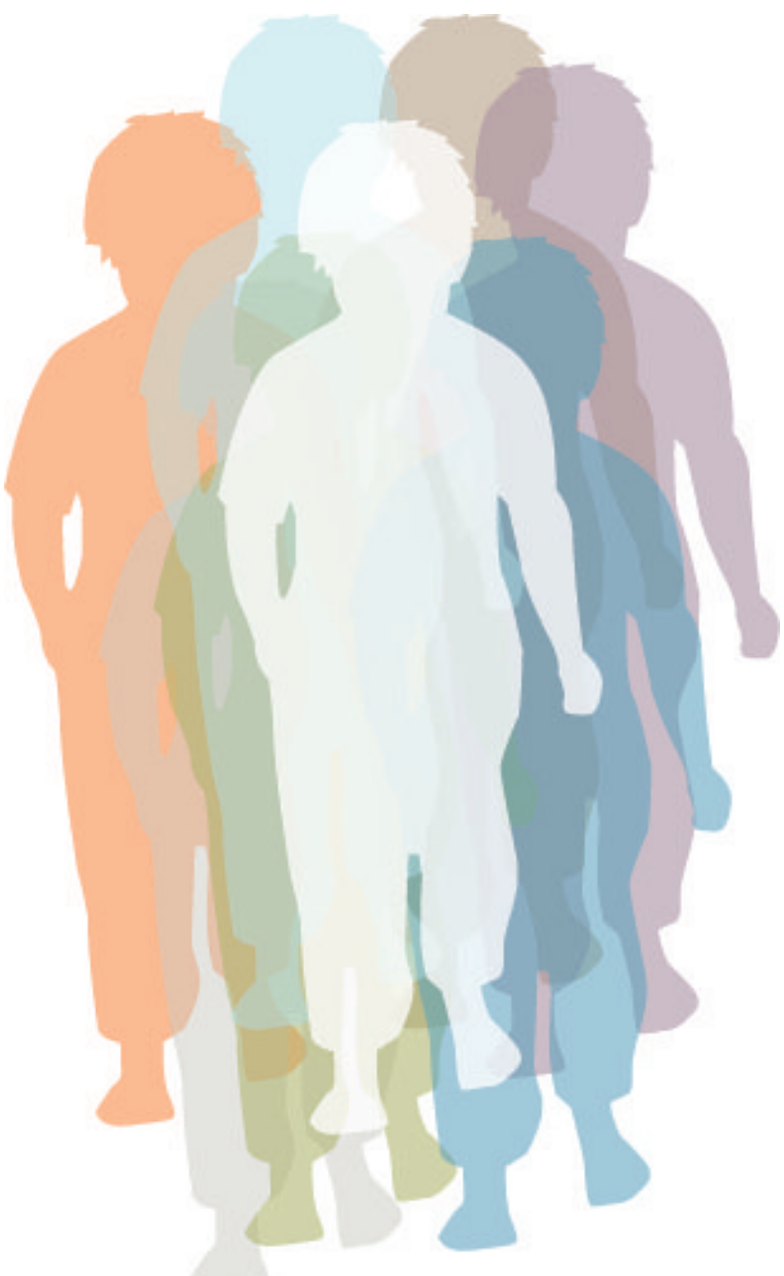
Medical Comorbidities in Autism Spectrum Disorders

A Primer for Health Care Professionals and Policy Makers



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March 2013

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www.treatingautism.co.uk

Registered Charity: No. 1113628, Limited Company Registered in England: No. 5594787

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First published March 2013 by Treating Autism Publications.

ISBN: 978-0-9575787-0-8

A pdf version of this publication is available from the Treating Autism website www.treatingautism.co.uk.
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Introduction

Many children and adults with a diagnosis of autism spectrum disorder (ASD) have comorbid health problems. Recent large-scale studies have confirmed that several medical conditions are significantly more prevalent in people with autism compared to the typical population. A detailed assessment conducted by the US Centers for Disease Control and Prevention demonstrated that **children with autism had much higher than expected rates of all of the medical conditions studied**, including: eczema, allergies, asthma, ear and respiratory infections, gastrointestinal problems, severe headaches, migraines, and seizures (Kohane et al., 2012).

Further studies from the US, Europe and Asia that carried out detailed clinical investigations confirmed that medical comorbidities were highly prevalent in children and adolescents diagnosed with ASD. Abnormal clinical findings were common and additional investigations revealed a high prevalence of medical disorders or manifestations, making it clear that ***"an appropriately extensive medical assessment is essential in all cases"*** (Isaksen et al., 2012; Mazurek et al., 2012; Memari et al., 2012; Kose et al., 2013).

Mortality is significantly increased in autism, with death rates being three to ten times higher than the general population (Bilder et al., 2012; Woolfenden et al., 2012). These deaths tend to be the result of medical comorbidities, such as epilepsy, gastrointestinal conditions and respiratory disorders (Shavelle et al., 2001; Pickett et al., 2006; Gillberg et al., 2010; Bilder et al., 2012; Woolfenden et al., 2012). One study found that deaths from gastrointestinal and respiratory disorders were 40.8 and 24.5 times higher, respectively, in moderately to severely affected patients versus typical peers (Shavelle et al., 2001). Another study that looked at the general health of adults with autism found that without intervention, those patients appear to be at significant risk for developing diabetes, coronary heart disease, and cancer (Tyler et al., 2011). Adults with developmental disabilities are also at much higher risk for osteoporosis and show severe degrees of bone demineralisation (Jaffe et al., 2001; Jaffe and Timell, 2003).

> "Treatment of comorbid medical conditions may result in a substantial improvement of quality of life both of the child and their parents. What investigations should be implemented can vary both within the autism spectrum and individually."
>
> *Isaksen et al., 2012 'Children with autism spectrum disorders: The importance of medical investigations.'*

> "Comorbidity is to be expected in autism spectrum disorders — directly or indirectly. Comorbid conditions may be markers for underlying pathophysiology and request a more varied treatment approach."
>
> *Isaksen et al 2012. 'Children with autism spectrum disorders: The importance of medical investigations.'*

Over time, anecdotal reports and opinions on what constitutes 'autism behaviours' have been adopted as unofficial criteria in the assessment of autistic patients; however, there is no evidence supporting the attribution of behaviours such as head banging, night waking, aggression and posturing to the pathophysiology of autism. In fact, there is substantial evidence to the contrary, as reflected in the consensus report from the American Association of Pediatrics (AAP) which states that, "Care providers should be aware that problem behavior in patients with ASDs may be the primary or sole symptom of the underlying medical condition, including some gastrointestinal disorders." (Buie et al., 2010). **Behaviours in the ASD population are often physical in origin, identifiable through investigation, and treatable or manageable through appropriate medical care.**

The AAP, in their widely distributed Autism A.L.A.R.M. (2004), encourages clinicians to listen to parents, because they "generally DO give accurate and quality information". However, like clinicians who are working

with communicatively-impaired ASD patients, parents or carers may also face communication barriers with their ASD child. Furthermore, parents may be unaware of the possible implications of the symptomatology, especially if at any point they have been told that behaviours are 'simply autism'. Nearly a third of adults with high functioning autism report that they don't receive appropriate medical care for physical health problems (Nicolaidis et al., 2012), and it is feared that suboptimal medical care is even more likely for those severely affected by autism and less able to communicate with clinicians and carers. In a survey conducted by Treating Autism, 81% of parents and carers of children with ASD and 76% of persons with ASD themselves (total N=220), stated that their health concerns had not been adequately investigated by health professionals. Further to this, 23.6% of total respondents had a medical diagnosis other than autism, yet that health concern had been dismissed in the past as 'autism' by their doctors. For 70.9% of these, the attribution of that comorbid medical problem to 'autism' by a health care professional had occurred more than 4 times (Treating Autism Survey, 2009).

Impairments in communication and social interaction are by definition core symptoms of ASD and play a role in the challenges clinicians face in diagnosing medical comorbidities. However, other symptoms and behaviours that frequently occur in autism have been erroneously assumed to be a result of autism itself, including anxiety, aggression, agitation, irritability, impulsivity, lack of focus, disturbed sleep, self-harming, self-stimulatory behaviours, lack of coordination, and visual, tactile and auditory oversensitivity. These so-called autistic behaviours have a substantial negative impact on not only the individual with autism, but also families and society as a whole (Sukhodolsky et al., 2008; Cheely et al., 2012; Geluk et al., 2011; Quek et al., 2012). Looking at one aspect of this extensive list, a recent study found higher than expected prevalence of aggressive behaviours, with parents reporting that 68% of their ASD children had demonstrated aggression to a caregiver and 49% to non-caregivers (Kanne and Mazurek, 2011). The costs, both human (Hodgetts et al., 2013) and monetary, (Knapp et al. 2009; Cidav et al. 2012; Barrett et al. 2012) reflected by these statistics are incalculable, especially given the ever-increasing autism rates (Centers for Disease Control and Prevention 2012; Zahorodny et al., 2012).

"The elevated mortality risk associated with ASD in the study cohort appeared related to the presence of comorbid medical conditions and intellectual disability rather than ASD itself suggesting the importance of coordinated medical care for this high risk sub-population of individuals with ASD."

Bilder et al., 2012 'Excess Mortality and Causes of Death in Autism Spectrum Disorders'

"Recognition from health care professionals that comorbid medical conditions such as GI disturbances, sleep disorders, and epilepsy were real issues that affect children with ASD was sorely needed."

Lajonchere et al. 2012 'Leadership in Health Care, Research, and Quality Improvement for Children and Adolescents With Autism Spectrum Disorders: Autism Treatment Network and Autism Intervention Research Network on Physical Health'

Widespread reports of severe medical conditions being attributed, without investigation and sometimes without physical examination, to autism behaviours have compelled the creation of this document in order to present relevant information to healthcare providers, policy makers and the wider audience. A summary of current research, including the positions of leading governmental and professional bodies, is hoped and expected to help bridge the knowledge and training gap, and as a consequence, decrease the premature attribution of physical symptoms to 'autism behaviours'. **Current research, shared below, offers support to health care and care providers in understanding the possible mechanisms, symptomatology, and consequences of common comorbidities in ASD, thus allowing improved patient care and reduced long-term costs.**

This document also provides a list of symptoms and behaviours that are indicative of health problems but often dismissed as 'autism', and offers common sources of such behaviour. Case studies highlight and contextualize some challenges faced in diagnosing this unique patient group and the possible outcomes of successful identification of underlying medical problems.

Current state of knowledge

Current neurological, immunological, metabolic, endocrinological, and epidemiological research is at the leading edge of a paradigm shift in our understanding of ASD. **Studies published in the last 12 months confirm many earlier findings** of widespread biomedical abnormalities in autism. While autism has been commonly assumed to be a neurodevelopmental and behavioural disorder, and kept within the boundaries of psychiatry and neurology, it is now increasingly recognised as a whole-body disorder, with the core deficits in communication, social interaction, restrictive/stereotypic behaviours, and other commonly seen behaviours that have been attributed to ASD, being surface manifestations of a systemic and complex disease process.

Scientific evidence is accumulating that challenges the previously held belief that autism is an in-born and unchangeable condition: numerous studies now confirm that a significant percentage of previously typically-developing children regress into autism, and also that some children present with decreasing symptoms, or even complete recovery from autism or "optimal outcome" (Fein et al., 2013) following intensive intervention (Barger et al., 2012; Ekinci et al., 2012; Eriksson et al., 2012; Pellicano, 2012). Fein et al.'s study in particular challenges the assumption that ASD is static and lifelong, and provides strong *"evidence that recovering from autism is indeed possible and opens up the possibility of improvement, even without optimal normalization."* (Ozonoff, 2013).

While further studies are under way to elucidate the exact reasons why some typical children may descend into autism, or why some lose their autism following intervention, it is now well established that **specific medical problems are associated with the severity of the condition** and that successfully addressing these comorbidities often leads to significant improvement in overall functioning. "*Several lines of research lend hope to the idea that biomedical treatments may someday improve the prognosis for a larger majority of children diagnosed with ASD.*" (Helt et al., 2008).

Some of the biomedical abnormalities found to date in ASD include, but are not confined to, neuroinflammation and immune dysregulation, abnormal gut flora, autonomic dysfunction, oxidative stress and mitochondrial dysfunction — all of which could have pathological consequences and clear negative impact on behavior and neurological functioning.

> "Allergic conditions are easily treatable; however, ASD children may be under-diagnosed and/or undertreated for allergic and other common childhood diseases, in part due to their impaired communication skills. Practicing physicians should be aware of the potential impact of allergic diseases on behavioral symptoms and cognitive activity in ASD children"
>
> *Jyonouchi, 2010 'Autism spectrum disorders and allergy: Observation from a pediatric allergy/immunology clinic'*

Neuroinflammation and immune dysregulation in ASD

There is firm evidence of immune dysfunction in individuals with autism. Results of numerous studies point to abnormal immune function, including on-going neuroinflammatory response. Several postmortem and in vivo investigations found chronic inflammatory processes in multiple areas of the brain and multiple studies have found a correlation between levels of immune dysfunction and severity of autistic symptoms (Vargas et al., 2005; Chez et al., 2007; Li et al., 2009; Morgan et al., 2010; Wei et al., 2011; Young et al., 2011; Suzuki et al., 2013). These observations resemble findings in other inflammatory and autoimmune disease states, in which elevations in levels of cytokines or autoantibodies are associated with the pathogenesis of neuroinflammation, neurotoxicity and neuronal injury, and subsequent behavioural and cognitive impairments, for example multiple sclerosis or HIV-induced neurological dysfunction.

CASE EXAMPLE 1 **Munair is a 5-year old boy with regressive autism. He was progressing reasonably well when he developed what looked like self-harming behaviour. Munair would frequently strike his jaw forcefully, always in the direction of the occiput. This would make a loud clunking noise. At the same time he developed a 'fondness' for jumping from higher and higher height. On examination he had bilateral purulent ear effusions. He was underweight and undernourished despite good intake. Amoxicillin was unsuccessful. Azithromycin helped significantly, but discontinuation led to recurrence. A five-day course of azithromycin followed by every other day dosing led to a sustained and substantial improvement. The jaw-striking and jumping was thought to be an attempt to unblock his ears.**

> "For patients with ASDs, a detailed history (including personal history of allergic disease, dietary history, and family history) and physical examination should be performed to accurately identify potential comorbid allergic disease."
>
> *Consensus Report, American Academy of Pediatrics, Buie et al., 2010*

In autism, findings of chronic inflammation and immune dysregulation throughout the central nervous system are accompanied by serum findings, all pointing to widespread dysregulation of immune mechanisms. Individuals with autism often display immune abnormalities in the form of altered cytokine profiles, autoantibodies, changes in immune cell function and abnormal mast cell activation (Molloy et al., 2006; Enstrom et al., 2009; Ashwood et al., 2011; Naik et al., 2011; Suzuki et al., 2011; Abdallah et al., 2012; Afaf El-Ansary and Al-Ayadhi, 2012; Theoharides et al., 2012b).

Addressing the immunological differences found in autism can often alleviate some of the core symptoms of the disorder and improve overall functioning of affected individuals (Gupta et al., 1996; Matarazzo, 2002; Boris et al., 2007; Sharma et al., 2012).

Allergic disorders in ASD: effects of allergies on behaviour, cognition and anxiety

Food and inhalant allergies, including frank atopic diseases, and food intolerances are common in autism (Kohane et al., 2012; Schieve et al., 2012). Furthermore, it has been demonstrated that a challenge with nasal allergens results in increase of autism symptoms in over half of children studied (Boris and Goldblatt, 2004) while treatment of allergies often results in improvement in behaviours such as anxiety, hyperactivity, and irritability, commonly attributed to 'being autistic' (Jyonouchi, 2010; Schieve et al., 2012; Chen et al., 2013).

Both IgE and non-IgE mediated allergic reactions are increasingly recognized causative factors of anxiety and mood disorders. As well, these allergic reactions contribute to difficulty focusing, irritability, tics, daytime fatigue and sleep problems in both children and adults.

Children with allergies suffering from learning disabilities, hyperactivity, fatigue, incoordination and irritability who are treated for their allergies show marked improvement in ability to learn, reduction of hyperactivity and incoordination, and ability to perform intelligence tests (Randolph, 1947; Millman et al., 1976; Price et al., 1990; Chen et al., 2012). The characteristic symptoms of allergic disorders may include bronchial asthma, allergic rhinitis, and atopic dermatitis, all of which may cause difficulty falling asleep as well as night waking due to difficult breathing, itching and scratching. These sleep disturbances lead to daytime inattention, irritability, and hyperactivity (Dahl et al., 1995; Shyu et al., 2012). Similarly, a large population-based study recently found that the presence of anxiety, aberrant mood and behaviours is considerably reduced in adults who receive allergy treatments compared to those left untreated (Goodwin et al., 2012).

According to a report by Neuroallergy Committee of the American College of Allergy, "***Allergic irritability syndrome is a concise, quantifiable way to define the decreased ability to concentrate, bouts of irritability and temper tantrums that sometimes occur as side effects of allergic rhinitis.***" (Klein et al., 1985).

It is now known that allergic diseases like atopic dermatitis and allergic rhinitis are characterised by an

CASE EXAMPLE 2 **Edward is a 14-year-old boy with a history of severe regressive autism. He presented with an 18-month history of altered behaviour. Sub-acute onset of self-harm, agitation, frequent night waking and latterly, aggression against others. Appetite was variable but largely maintained. Stools were reported as normal on the background of long-standing constipation. GP had referred to paediatrician, who referred to a paediatric gastroenterologist, who referred on to a neurologist. He was commenced on carbamazepine for mood-stabilisation. At consult he was agitated, preferred to sit, but frequently stood straight, pacing. He required constant one to one supervision, provided by his father. Edward struck his father twice during the consultation. He had no speech. No further examination was possible. He was re-referred to gastroenterology, referred on to a general surgeon and underwent a semi-urgent gastric fundoplication. Aggressive behaviour has not recurred.**

imbalance of the hypothalamus-pituitary-adrenal axis (HPA) and the sympathetic axis, which in turn can influence behaviour and cognition. These effects are most likely mediated through effects of histamine on adrenaline release and also via direct activation of HPA by pro-inflammatory molecules released by mast cells, which have long been implicated in stress-induced immune responses (Scaccianoce et al., 2000; Kalogeromitros et al., 2007; Liezmann et al., 2011).

Mastocytosis or mast cell activation syndrome is a spectrum of rare diseases characterized by increased number of activated mast cells in many body organs. **Children who are affected by this disorder appear to have autism at a rate tenfold higher than that of the general population children** (Angelidou et al., 2011). It has been proposed that excessive activation of mast cells could be the central pathogenic mechanism in at least some types of idiopathic autism. This is currently being investigated by Tufts University researchers, with preliminary treatment trials of mast cell blocking agents yielding promising results (Theoharides et al., 2012a; Theoharides et al., 2012b).

Given the high prevalence of allergic diseases and non-IgE mediated hypersensitivity reactions and mast cell over-activation in autism, as well as confirmed HPA and sympathetic over-activation (see following section), it seems likely that many aberrant behaviours that are frequently characterized as 'autism' are being caused or exacerbated by potentially treatable and preventable allergic reactions.

Health professionals should be aware that when a child or adult with autism presents with 'autistic irritability' or increased anxiety, inability to fall or stay asleep, inability to concentrate, hyperactivity and daytime fatigue, the possibility of allergic and hypersensitive conditions should be considered (Jyonouchi, 2010; Goodwin et al., 2012; Theoharides et al., 2012b).

Non-celiac food sensitivity and ASD

Recent large-scale double-blinded studies have confirmed the existence of non-celiac wheat sensitivity as a new clinical entity. Patients with a history of allergies and atopic diseases are more likely to suffer from non-celiac food sensitivity (Massari et al., 2011; Carroccio et al., 2012). Since children with autism are almost twice as likely as controls to suffer from atopy and allergies, possible wheat sensitivity in those children needs to be considered, especially when irritable bowel syndrome symptoms are present (see following section) (Menchetti et al., 1995; Sandler et al., 2000; Schieve et al., 2012). A joint clinical trial currently being undertaken by Massachusetts General Hospital and Second University of Naples is focusing on identifying a clinical diagnostic biomarker for non-celiac gluten sensitivity. It should be noted that Carrocio and colleagues (2013) found that the main histological characteristic of non-celiac wheat sensitivity was mucosal eosinophil infiltration. Histological findings of prominent mucosal eosinophil infiltration have been observed in a high percentage of children with autism, and have been found to be significantly lower in children following a gluten-free diet (Ashwood et al., 2003; Chen et al., 2010). The most recent Cochrane systematic review of gluten- and casein-free diets for autistic spectrum disorder, published in 2009, recommended that large scale, good quality randomised controlled trials are needed,

> "If the gastrointestinal disorder is recognized and medical treatment is effective, the problem behaviours may diminish. When abdominal pain or discomfort is a setting event, psychotropic medications are likely to be ineffective and may even aggravate the problem if they have adverse gastrointestinal effects."
>
> *Consensus Report, American Association of Pediatrics - Buie et al., 2010*

CASE EXAMPLE 3 **Christopher is a 20-year old male with moderate to severe autism. He presented with sudden onset self-harm and destructive behaviour. Over three years he was trialled on various neuroleptics, to minimal effect. Chest infections had become progressively worse over the three-year period. Chest exam suggested right lower consolidation. Chest CT revealed consolidation. Only partial resolution with antibiotics was achieved. Bronchoscopy revealed a 15mm twig central to the consolidation. Removal, prednisolone and a protracted course of azithromycin resolved the consolidation, and his self-harm and destructive behaviour also resolved. Christopher had not localised to the pain source nor had he developed pyrexia.**

CASE EXAMPLE 4 **David is a 34-year old male with mild to moderate autism. He presented with a two-month history of unexplained aggressive outbursts. Despite reasonable communication skills he could not explain the outbursts of rage. Examination was unremarkable. Routine investigations revealed H.Pylori. His rage episodes resolved after eradication therapy and one month on a proton pump inhibitor.**

however from the existing trial evidence it concluded that ***"the diet poses no disbenefit or harm"***, and it identified positive effects of the this diet relating to improvement in overall autistic traits, social isolation, and overall ability to communicate and interact (Millward et al., 2008). A more recent review of the literature on the benefits of a gluten free diet in autism found that ***"although not wholly affirmative, the majority of published studies indicate statistically significant positive changes to symptom presentation following dietary intervention"*** (Whiteley et al., 2012).

Autoimmunity in ASD

The connection between autism and autoimmune disorders is gaining increasing support with a number of studies demonstrating a high incidence of autoimmune conditions in autism and an association between serum levels of various autoantibodies and severity of autistic symptoms (Mostafa and Al-Ayadhi, 2011; Frye et al., 2012; Mostafa and Al-Ayadhi, 2012; Chen et al., 2013). Autoantibodies to folate receptors for example are suspected to play a pathological role in some forms of idiopathic autism because of their negative effects on cerebral folate metabolism and well-known involvement in other neurodevelopmental syndromes (Hyland et al., 2010; Ramaekers et al., 2012).

Consistently, family history of autoimmune diseases is significantly higher in autistic children than in general population (Sweeten et al., 2003; McDougle and Carlezon, 2013).

The combination of these findings has led many researchers and clinicians to suggest that autoimmune mechanisms could be a causative or contributing factor in at least a subset of individuals with autism.

Immune system in ASD: translational research and clinical evidence

Autism-related symptoms and behaviours can be induced in offspring by maternal exposure to infection and maternal immune mediators. These outcomes have been observed in both animal experiments and maternal clinical histories. **Animal models show clear connections between anxiety, abnormal social behaviours and levels of proinflammatory cytokines.** Correcting immune abnormalities in post-exposure experiment animals with immune-modulatory treatments results in normalisation of immune function, and more importantly, improvements in cognitive function and complete and lasting reversal of abnormal autism-related behaviours (Kipnis et al., 2004; Hsiao et al., 2012).

> "For patients with ASDs, a detailed history (including personal history of allergic disease, dietary history, and family history) and physical examination should be performed to accurately identify potential comorbid allergic disease."
>
> *Consensus Report, American Academy of Pediatrics, Buie et al., 2010*

Activation of the immune system is known to lead to functional changes in the central and autonomic nervous system and to impact behaviour. Prolonged peripheral inflammation, even when subclinical, causes 'sickness behaviours' in animals characterized by reduced affection and social motivation, increased anxiety, avoidance of novel situations, repetitive behaviours, reduced exploration, self-imposed dietary restrictions and many other symptoms that mirror those seen in autism (Kohman et al., 2009; Johansson, 2012; Yee and Prendergast, 2011).

Similarly, the presentation of patients suffering from chronic inflammatory or autoimmune disease, or undergoing cytokine therapy, demonstrates that

CASE EXAMPLE 5 **Max is a 13 year old by with high functioning autism. He presented with a 2-3 year history of increasingly labile mood, obstinance and some mild cognitive impairment. Behaviour and performance had begun to affect his school placement. Examination revealed grossly pitted and erythematous tonsils. Bloods revealed an ASOT of 800 (nr > 200), mildly elevated platelets of 420 (nr > 400) and marginally elevated ESR of 11 (nr > 10). Results remained abnormal over time with only partial response to antibiotics. Max was referred to ENT, and subsequently underwent a tonsillectomy. Within two weeks mood improved, obstinance ceased and his school grades returned to normal.**

immune dysregulation can impact behavior, moods, personality and cognitive function. Addressing peripheral infections (for example in the gastrointestinal system or sinuses) calming autoimmune reactions, or discontinuing therapy with inflammation-inducing agents, often leads to reversal and normalization of symptoms and restoration of brain function (Siegel and Zalcman, 2008; Myint et al., 2009).

A link between immune dysfunction and autism is further exemplified by a recent multi-genome analysis study, which found links between genes that predispose individuals to **aberrant immune response to infections and risk of developing autism** (Saxena et al., 2012), as well as two separate findings from large European birth cohorts, which both found perturbed immune responses and pro-inflammatory biomarkers in mothers and newborns who later develop autism (Abdallah et al., 2012; Brown et al., 2013).

In this context it must be mentioned that the most rigorous and largest population-based twin study of autism done to date has found that *"susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component"* and *"although genetic factors also play an important role, they are of substantially lower magnitude than estimates from prior twin studies of autism."* (Hallmayer et al., 2011). Furthermore, the three largest genome-wide association studies performed on more than 3000 individuals in total, have failed to detect any specific gene association with any consistency across the studies (Wang et al., 2009; Weiss et al., 2009; Pinto et al., 2010). These studies identify a small number of ASD individuals with novel genetic changes called Copy Number Variantion or CNV. However, as Pinto et al. states, "the population attributable risk ... is estimated to be 3.3%". This says, in effect, that 96.7% of ASD cannot be attributed to these genetic changes.

Abnormal bacterial flora and gastrointestinal comorbidities in ASD

Gastrointestinal problems are a commonly found in autism and may be related to problem behaviours, sensory overresponsitivity, dysregulated sleep, anxiety and irritability (Heijtz et al., 2011; Mazurek et al., 2012; Schurman et al., 2012; Chandler et al., 2013). Results from a large-scale population-based study conducted by the US Centers for Disease Control and Prevention showed that children with autism, in addition to many other unmet health needs, were twice as likely as children with ADHD, learning disability or other developmental delays, to have experienced frequent diarrhoea and/or colitis during the past year. They were also seven times more likely to have experienced these gastrointestinal problems than typical controls (Schieve et al., 2012).

> "The role of immune responses in the pathogenesis of gastrointestinal disorders in individuals with ASDs warrants additional investigation."
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> *Consensus Report, American Academy of Pediatrics, Buie et al., 2010*

Over the past several years there has been an increased recognition of gastrointestinal comorbidities among individuals with autism, including increased intestinal permeability, diarrhoea, constipation, gastroesophageal reflux, digestive enzyme deficiency and bacterial dysbiosis (Horvath et al., 1999; Wasilewska et al., 2009; de Magistris et al., 2010; Kushak et al., 2011; Williams et al., 2011; Persico and Napolioni, 2012). Recent research has also confirmed that, contrary to commonly-held beliefs, presence of **gastrointestinal dysfunction in children with autism is not associated with distinct dietary habits or medication status**, and parental reporting of any GI dysfunction in their children is highly concordant with later clinical diagnosis of that dysfunction (Gorrindo et al., 2012).

The strong correlation of gastrointestinal symptoms with severity of autism indicates that children more severely affected by autism are likely to have severe gastrointestinal symptoms (Adamset al., 2011, Wang et al., 2011; Gorrindo et al., 2012). An American Academy of Pediatrics consensus paper recommends that health care providers should be alerted to the

CASE EXAMPLE 6 **Steven is a 5-year old boy with marked regressive autism. He suffered sleep disturbance, self-selected dietary restriction and marked hyperactivity. He could follow no commands. He ate only dry, starchy food. Parents had placed a plastic shield over their TV due to Steven continuously slapping the screen. On examination he had marked tonsillar enlargement with marked erythema, and reactive anterior cervical chain lymphadenpathy. Bloods showed mildly raised inflammatory markers and elevated eosinophils. He was commenced on a protracted course of co-amoxiclav for strep throat. Within three weeks he had calmed, seemed happier and widened his diet. He began obeying one and two stage commands. Parents reduced potential allergens in the bedroom and he began sleeping through the night.**

CASE EXAMPLE 7 **Joseph is a pleasant 10-year old boy with regressive autism. Visual learning was markedly improving, but speech and listening skills were disproportionately behind. He had a long history of ear infections with grommet insertion twice before. Further ENT review revealed failed grommets, reinsertion with titanium grommets failed too. He did not respond to allergy management, a trial of antifungals and a protracted course of azithromycin. He was duly referred to an immunologist, and subsequently found to have a Mannose-Binding Protein deficiency. He has made good progress on long-term prophylactic antibiotics.**

behavioral manifestations of gastrointestinal disorders in patients with autism, ***"as those can be atypical and evident only as a change in behaviour, thus presenting a significant challenge to both parents and health care providers."*** (Furuta et al., 2012). This consensus paper identified that, in children with ASDs:

1. subtle or atypical symptoms might indicate the presence of constipation;
2. screening, identification, and treatment through a deliberate approach for underlying causes of constipation is appropriate;
3. diagnostic-therapeutic intervention can be provided when constipation is documented;
4. careful follow-up after any intervention be performed to evaluate effectiveness and tolerance of the therapy.

In individuals with autism, atypical presentations of common gastrointestinal problems can include emergence or intensifying of seemingly non-related 'autistic' behaviours such as self-harm, irritability, aggression, strange posturing or movements (Buie et al., 2010). Because autonomic disturbances are common in autism, the posturing and guarding responses typically seen in non-ASD children with abdominal disease might be decreased in individuals with autism. Practitioners need to bear in mind the high mortality rate from digestive diseases in autism.

In another paper, the American Academy of Pediatrics stresses the need for appropriate investigations:

"Despite the magnitude of these issues, potential GI problems are not routinely considered in ASD evaluations. This likely reflects several factors, including variability in reported rates of GI disorders, controversies regarding the relationship between GI symptoms and the putative causes of autism, the limited verbal capacity of many ASD patients, and the ***lack of recognition by clinicians that certain behavioral manifestations in children with ASDs are indicators of GI problems*** *(e.g. pain, discomfort, or nausea). Whether GI issues in this population are directly related to the pathophysiology of autism, or are strictly a comorbid condition of ASD remains to be determined, but clinical practice and research to date indicate the important role of GI conditions in ASDs and their impact on children as well as their parents and clinicians."* (Coury et al., 2012).

> "Developing effective treatments and improving care for individuals with ASDs throughout the life span remain urgent priorities."
>
> *James M. Perrin, MD, Harvard Medical School, President-elect of the American Academy of Pediatrics*

Analyses of the bacterial flora composition of individuals with autism have frequently revealed the presence of abnormal bacteria that are absent from healthy controls, as well as translocation of bacterial species to parts of gastrointestinal system that are not host to those bacteria in healthy individuals (Finegold et al., 2002; Parracho et al., 2005; Ekiel et al., 2010; Finegold et al., 2010; Williams et al., 2012).

Metabolic/biochemical changes found in the urine of individuals with autism further confirm the gut microbiota abnormalities revealed by stool and ileal tissue investigations (Yap et al., 2010; Ming et al., 2012). Endotoxemia has been observed in patients with autism, and the levels of bacterial toxins in the blood have been found to correlate to severity of

CASE EXAMPLE 8 **Luke is a 5-year old boy with regressive autism. With intensive intervention he made good progress, but marked anxiety in social situations remained. Parents complained that he suffered uncontrolled terror when he even went near a busy play park. Parents had resorted to taking him very early in the morning. On examination he had a pulse of 100 BPM, with further increase upon questioning/challenging. He was commenced on 20mgs of propranolol in the morning and 10mgs in the afternoon. Immediate resolution of social anxiety ensued. Within one week Luke was playing for 30 minutes in a busy park. He has made further advancements in development since.**

autism symptoms (Emanuele et al., 2010). This is believed to result from both the increased presence of pathogenic bacteria and the increased intestinal permeability seen in autism. A small treatment trial of oral vancomycin noted a decrease in autism-related behaviours following a course of this antibiotic. This observation, which has since been mirrored by numerous clinical reports, points further to a possible correlation between levels of pathogenic bacteria and severity of autistic symptoms (Sandler et al., 2000).

As discussed in the previous section, pain and sickness have profound influences on mood, cognition, and behaviour, including sociability and communication. Equally, chronic inflammation and infections of the gastrointestinal tract are associated with increased circulatory levels of pro-inflammatory cytokines with direct effect on behaviour, including anxiety, motivation, socialisation, avoidance of novel situations, and adherence to routine and repetitive actions. Pathogens or mediators derived from the immune system interact with peripheral neural pathways, such as the intestinal enteric nervous system and the autonomic nervous system, and consequently affect brain function (Sharkey and Kroese, 2000; Goehler et al., 2005; Goehler and Gaykema, 2009). In animal models of autism, animals exposed early in life to bacterial toxins develop autistic traits (MacFabe et al., 2011; Willette et al., 2011; Baharnoori et al., 2012; El-Ansary et al., 2012). Subclinical gastrointestinal infections, such as Small Intestinal Bacterial Overgrowth are known to induce anxiety and aberrant behaviours in previously healthy adult animals (Lyte et al., 1998; Lyte et al., 2006).

Oxidative stress, acquired mitochondrial dysfunction and metabolic abnormalities in ASD

There is increasing evidence that mitochondrial dysfunction, perturbation in sulfur and amino acid metabolism, and high levels of oxidative stress are common in persons affected by autism. Elevations in metabolic markers of oxidative stress as well as reduced levels of glutathione and other cellular antioxidants have been found in many areas of the body, including the brain and primary immune cells (Chauhan et al., 2012; Ghanizadeh et al., 2012; Rose et al., 2011; Rose et al., 2012). Reactive oxygen species are destructive to cells and organs, and elevated oxidative stress has been implicated in autoimmune, inflammatory, cardiovascular and neurodegenerative diseases, and cancer.

> "Perpetuating the myth of autism as a primarily genetic disorder is a disservice to those who might benefit from treatment and diverts attention from nongenetic causes."
>
> *Prof Richard Deth, Northeastern University, Boston*

A substantial percentage of autistic patients display markers of abnormal mitochondrial energy metabolism, such as elevated lactate, pyruvate, and alanine in blood, urine and/or cerebrospinal fluid, as well as serum carnitine deficiency (Filipek et al., 2004; Oliveira et al., 2005; Frye et al., 2013). In the majority of cases this abnormal energy metabolism cannot be linked to specific inborn mitochondrial disease, or another primary inborn error of metabolism. It has therefore been suggested that in autism, abnormalities in mitochondrial function could be a downstream consequence of immune dysfunction (Palmieri and Persico, 2010; Rossignol and Frye, 2011). Insufficient mitochondrial energy production could both result from and contribute to cellular oxidative stress and chronic inflammation in autism.

Raising antioxidant levels and/or metabolic precursors and supporting mitochondrial function have been proposed as treatment avenues. Small clinical trials of antioxidants such as carnosine and

CASE EXAMPLE 9 **Sally is an 11-year old girl with late regressive autism. She presented with a six-month history of worsening self-harm, head-banging, obsessions and episodic aggression against others. Previously Sally was placid with episodic obsessional behaviours. On examination Sally held her head frequently and disliked bright lights. When asked where it hurts Sally localised to the top of her head. Apart from some mild right iliac fossa tenderness there was little else to find. Bloods showed ASOT of 800 (nr >200), ESR of 12 and platelets of 350. Rheumatoid Factor was markedly elevated at 104 (nr >14). She was commenced on co-amoxiclav and prednisolone and referred to Paediatric Neurology and Rheumatology. Within three days her symptoms had reduced substantially. There was no self-harm, no aggression and Sally returned to her placid self. Speech was significantly improved, and Sally was able to express widespread joint pain.**

N-acetyl-l-cysteine, mitochondrial agents such as carnitine, and metabolic precursors such as methylcobalamin and folinic acid have shown promising results in autism (Chez et al., 2002; James et al., 2009; Rossignol and Frye, 2011; Ghanizadeh et al., 2012; Hardan et al., 2012).

Autonomic nervous system dysfunction (dysautonomia) in ASD

In recent years, an increasing number of researchers and clinicians have focused their attention on abnormalities of the autonomic nervous system (ANS) within the ASD population.

Elevated sympathetic and lowered parasympathetic activity is frequently present in children and adults with autism **whether or not they have more obvious outward symptoms or signs of autonomic abnormalities** (Toichi and Kamio, 2003; Ming et al., 2005; Fan et al., 2009; Patriquin et al., 2011; Cheshire, 2012; Daluwatte et al., 2012).

> "Given the extreme heterogeneity of ASDs and other neurodevelopmental disorders, effective treatments for individuals with ASDs will likely benefit from a personalized medicine approach that takes into account individual differences in etiologic and phenotypic characteristics."
>
> *Lajonchere et al. 2012 'Leadership in Health Care, Research, and Quality Improvement for Children and Adolescents With Autism Spectrum Disorders: Autism Treatment Network and Autism Intervention Research Network on Physical Health'*

It has been suggested that manipulating autonomic function could be a possible treatment avenue for aggression, anxiety and irritability, as well as the core symptoms of autism and cognitive functioning (Ratey et al., 1987; Narayanan et al., 2010; Beversdorf et al., 2011; Bodner et al., 2012). Following very promising pilot trials on adults with autism, which demonstrated that adrenergic antagonist propranolol improves the core features of the disorder, such as impaired social interaction and communication, randomised controlled trials are currently underway at the University of Missouri, MU Thompson Center for Autism and Neurodevelopmental Disorders.

Seizure disorders in ASD

Prevalence of seizure disorders is significantly higher in people with ASD than is the norm and epilepsy is a contributing factor to the elevated mortality risk seen in autism, making detection and treatment of this medical comorbidity in autism of utmost importance (Hughes and Melyn, 2005; Mouridsen et al., 2011). This is especially relevant in the context of subclinical epileptiform activity being found in a majority of individuals with autism, even in the absence of clinical seizure disorder. When epileptiform activity is present in the ASDs, therapeutic strategies such as antiepileptic drugs, steroids, and even neurosurgery aimed at its control can often lead to a significant improvement in language and autistic behaviours, in addition to reducing seizure activity (Lewine et al., 1999; García-Peñas, 2005; Muñoz-Yunta et al., 2008). ***"Given the frequency of seizure disorders in this population, a high index of clinical suspicion should be maintained for subtle symptoms of seizures."*** (Kagan-Kushnir et al., 2005).

CASE EXAMPLE 10 **Jameel is a 5-year old boy. He developed normally until 15 months of age when he experienced 3 weeks of continuous fever. His communication, socialisation and behaviour became affected from that point; he lost all speech and eye contact, and presented with marked sleep disturbance, and self-restricted diet. Gastrointestinal symptoms were present early on including a distended abdomen, alternating diarrhoea and constipation and marked malodour. He became prone to ear infections, had chronic dermatitis, head banging every 2 hours, cracked lips, allergy shiners.**

At presentation Jameel was underweight, distressed, uncooperative and unhappy. Jameel received a diagnosis of autism at age 2 years and 7 months. A number of laboratory tests were undertaken and several issues were identified: elevated total IgE and eosinophil count (allergy against foods and inhalants identified), low Natural Killer Cell Count, markedly elevated ASLO titer, deficiencies in iron, vitamin D, Omega 3, together with raised proprionic acid, hippuric acid and 4-hydroxyphenyacetic acid.

Successful treatment consisted of dietary exclusion, good environmental hygiene, correction of deficiencies, and combination antimicrobials for intestinal bacterial overgrowth. Over three months sleep normalised, vocalisation, eye contact and understanding improved. Head banging stopped. Bowels improved.

Approaching comorbidity in the ASD patient: Medical Considerations

Up until recently, scientific consensus suggested autism progresses to a predetermined outcome regardless of medical intervention. Advice to patients, guardians and the wider audience has reflected such consensus. Now the consensus has changed, and so must the awareness.

Until more definitive answers pertaining to the pathophysiology of autism are available, frontline physicians are charged with treating, as best as they can, whatever medical illnesses a patient may have, whether they be comorbid, or part of the underlying pathology. The importance and value of such treatment has been highlighted by recent authoritative studies.

Managing comorbid illness in the autistic patient carries a multitude of challenges. Communicating pain, processing pain or tenderness, level of baseline agitation, lack of a coherent history, and other factors can all contribute to a challenging assessment. In all likelihood, such challenges reflect the substantial respiratory, gastrointestinal and neurological morbidity and mortality rates that are consistently reported.

The chart below is an attempt to improve recognition of common problems encountered when autistic patients present with comorbid health issues. These recommendations may seem somewhat basic considerations when dealing with a communication-challenged patient of any age, however, increasing reports of premature attribution of physical health issues to the autism phenotype and the consequences thereof, make it prudent to highlight the following:

1 Behaviours which may indicate an underlying comorbid illness include:

- Sudden change in behaviour
- Loss of previously acquired skills
- Irritability and low mood
- Tantrums and oppositional behaviour
- Frequent night-waking or general sleep disturbance
- Change to appetite or dietary preferences
- Heightened anxiety and/or avoidance behaviours
- Repetitive rocking or other new repetitive movement
- Sensory hyper-responsitivity: hyperacusis, tactile defensiveness, sensitivity to light
- Covering ears with hands
- Teeth grinding
- Posturing or seeking pressure to specific area
- Behaviour around evacuation
- Aggression: onset of, or increase in, aggressive behavior
- Self-injurious behaviour: biting, hits/slaps face, head-banging, unexplained increase in self-injury
- walking on toes
- Constant eating/drinking/ swallowing (‘grazing’ behavior)*
- Facial grimacing, wincing, tics*
- Frequent clearing of throat, swallowing*
- Mouthing behaviours: chewing on clothes*
- Tapping behaviour: finger tapping on throat*
- Sobbing ‘for no reason at all’*
- Vocal expressions of moaning, groaning, sighing, whining*
- Agitation: pacing, jumping up and down*
- Blinking, sudden screaming, spinning and fixed look **

2 Pain can be acute or chronic, progressive or static.

3 Common sources of pain and discomfort include:

- Headache
- Earache
- Toothache
- Sore Throat
- Reflux
- Oesophagitis
- Gastritis
- Colitis
- Soft or hard stool constipation (underlying cause will be relevant)
- Small Intestinal Bacterial Overgrowth
- Musculoskeletal injury or disease
- Seizure Disorder (including subclinical crisis**)
- Allergy Disorder

* from Buie et al., 2010, ** from: Munoz-Yunta et al., 2008.

Conclusion

Medical comorbidities are much more prevalent and difficult to recognise in patients with autism than in the general population. The failure to identify such comorbidities is due in part to communication impairments and ambiguous symptomatology, but widespread under-diagnosis is also the result of commonly held beliefs that aberrant behaviours and symptoms are 'just a part of autism'. As a result, these pathologies are often left untreated.

All of the discussed medical comorbidities and consecutive pathological processes can negatively impact behaviour, socialisation, communication, cognitive function and sensory processing of individuals with autism. It is also becoming increasingly clear that the medical abnormalities that underlie autism are not stagnant or transient, but tend to be chronic and in many cases, if left unrecognised and untreated, progressive. Accurate diagnosis and treatment often results in improved level of functioning and decreased severity of symptoms. Recognition that problem behaviours might indicate an underlying medical condition will facilitate diagnosis and treatment and ultimately improve the quality of life for many individuals with autism. As well, correctly identifying and addressing medical comorbidities in autism will help reduce the immense emotional, physical and financial burden on families and carers, and is fiscally responsible to the wider society.

Children and adults with autism have an increased need for paediatric and/or specialist services, both for their core functional deficits and concurrent medical conditions. Appropriate and individualised medical assessment must be carried out in all cases, including a documented clinical examination.

CASE EXAMPLE 11 **Maryam is a 4-year old girl with regressive autism. At presentation she suffered frequent night-waking, episodic distress and, on direct questioning, posturing behaviour. Stools were malodorous, variable in consistency and could cause some discomfort. Developmentally, Maryam had a few words and was making slow progress. Mum felt the slow progress was due to her being in some sort of pain, and not sleeping properly. On examination, she looked uncomfortable. She was pale, with dry skin. There was slight right iliac fossa tenderness. Bloods revealed an ESR of 45 and iron deficiency anaemia. She was referred to a tertiary gastroenterologist who advised a gluten, casein and soya free diet. Symptoms improved significantly. She began sleeping through the night, passing normal bowel motions and looked brighter. Speech and general development improved. ESR fell to 25 after 2 months, 19 after 4 months and after one year reached 9.**

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CASE EXAMPLE 12 **Ivan is a 5-year old boy with regressive autism. He developed normally as a baby, including normal speech (bilingual) development. He started presenting with unusual behaviours at 18 months, including tip-toe walking, hand flapping, motor stereotypies. Lost previously acquired speech. Diagnosis of autism received at 1 year and 9 months. Ivan's gastrointestinal problems started around 24 months of age. Stools started to become mushy, malodorous, and light in colour. Ivan suffered from recurrent Herpes infection on the hands, causing permanent scarring.**

Recently Ivan presented with an acute onset of irritability, hyperactivity, sleep disturbance and occasional incontinence. His obsessional behaviours were marked. He was seen by rheumatology consultant, who undertook bloods. ASOT and Anti-DNAse B were positive. He was duly commenced on co-amoxiclav and his new symptoms resolved rapidly. Ivan's speech improved, and he became more socially engaged. He is currently under the care of rheumatology for PANDAS, and is reported as doing well.

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"Caring for youths with autism spectrum disorder can be overwhelming for some primary care physicians because of the multiple comorbid conditions that often accompany ASD… But treating these associated health issues often helps children with ASD feel better and can improve their behavior and performance in school."

Dr James Perrin, Professor of Pediatrics, Harvard Medical School, President–elect of the American Academy of Pediatrics

"This study reveals that medical disorders or manifestations are highly prevalent in children and adolescents diagnosed with ASD. Abnormal clinical neurological findings were quite common, and we found a high degree of pathology as a result of the additional medical investigations... This means that an appropriately extensive medical assessment is essential in all cases."

Isaksen et al., 2012 'Children with autism spectrum disorders — The importance of medical investigations'

"Care providers should be aware that problem behavior in patients with ASDs may be the primary or sole symptom of the underlying medical condition."

Consensus Report, American Academy of Pediatrics, Buie et al., 2010

"Many individuals with ASD have symptoms associated with underlying medical conditions, including seizures, sleep problems, gastrointestinal (GI) disorders, psychiatric conditions, nutritional deficiencies, and metabolic conditions; when left untreated, these conditions may not only compromise general health but also have clear effects on behavior, development, and educational outcomes for individuals with ASD."

Lajonchere et al. 2012 'Leadership in Health Care, Research, and Quality Improvement for Children and Adolescents With Autism Spectrum Disorders: Autism Treatment Network and Autism Intervention Research Network on Physical Health'

"We need to empower primary care physicians to know that they already have the skill set to work with children who have autism… Doctors can address these co-occurring behaviors head-on. It will make a positive difference."

Darryn M. Sikora, PhD. pediatric psychologist, Providence Child Center

"Autism is what we call a mosaic disease, it has many different facets to it… if you look into the literature, you'll find that autism isn't just a sort of neuropsychiatric, behavioural, and social disorder… It is a systemic disease, but the most obvious effect is the social and behavioural, and so it tends to be associated with that... What we have to do now using our modern technology is to take a step back, look at the whole problem as a systemic problem, and see how all the abnormal interactions that are occurring in the different organ systems in the body might impact on brain development and to give us the symptoms of autism, which are becoming all too familiar."

Prof Jeremy Nicholson, Chair In Biological Chemistry, Head of Department of Surgery and Cancer, Imperial College London

"Sudden and unexplained behavioral change can be the hallmark of underlying pain or discomfort. Behavioral treatment may be initiated as the possible concurrent medical illness is being investigated, diagnosed (or excluded), and treated, but the behavioral treatment should not substitute for medical investigation."

Consensus Report, American Association of Pediatrics, Buie et al. 2010

ISBN: 978-0-9575787-0-8