**Co morbidity in Asperger Syndrome: A review of the literature**

*Introduction*

Autism is a term utilized for a number of developmental disabilities called Autism Spectrum Disorder (ASD). ASD’s have become a centrepiece for research into mental health, medical and educational studies worldwide. Lin, Tsai, Rangel, & Adolphs (2012) reported that the classification of ASD as neuro-developmental pervasive disorders means that multiple areas of functioning are impaired which consequently affects the individual throughout their lifespan. ASD is one of the most common neuro-developmental disorders, whereby the estimated incidence rate is 1 in every 88 children (Baio, 2012). ASD’s usually emerge in the first three years of a child’s life. They are characterised by a triad of deficits involving communication, reciprocal social interaction, and restricted and repetitive patterns of behaviour, interests and activities. Polong (2010) stated that the symptoms of ASD’s can vary, and can often range from mild to severe but all children on the spectrum display deficits in social interaction, verbal and nonverbal communication and can exhibit repetitive behaviours and have fixated/limited interests.

With regard to ASD’s, professionals mostly diagnose patients with specific classifications from the Diagnostic and Statistical Manual (DSM-IV-TR). The spectrum consists of the following conditions: Autistic Disorder, Asperger syndrome (AS), Childhood disintegrative disorder (CDD), Rett’s Disorder and Pervasive development disorder (not otherwise specified).

In order to establish a diagnosis of AS, the DSM-IV requires, as for ASD, the presence of at least two symptoms of impaired social interaction and at least one symptom of restricted, repetitive behaviour (APA, 2000). Even though the majority of individuals with a clinical diagnosis of AS have excellent verbal ability and normal/high intelligence, the main difficulties in social interaction and communication can have a serious impact on the individual with regard to their mental health and psychosocial functioning (Lugnegard, Hallerback and Gillberg, 2011). Within the broad category of ASD’s, AS and High Functioning Autism (HFA) are two closely related conditions that share similar characteristics (Mazzone et al. 2013).
However, in the most recent DSM-5, AS is categorised under ASD with essential equivalence to HFA and the AS name has been removed as a separate entity (APA, 2013). Therefore, individuals, caregivers and health care professionals are now worried that the drop of the specific AS diagnosis may result in the loss of individualized, customized, reimbursable, suitable and appropriate services for individuals with AS (Sticher et al. 2010). Current estimates reveal that AS occurs at a rate of about 2.5/10,000 as compared to 60/10,000 for all ASD’s (Toth & King, 2008).

The diagnostic criteria for AS does not include mood disorders such as anxiety (45% prevalence in AS; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000) and depression (25-34% prevalence in AS; Mayes, Calhoun, Murray, Ahuji & Smith, 2011). Along with obsessive compulsive disorder (25% prevalence in AS; Mukaddes & Atwood, 2006); even though a large proportion of individuals with AS are affected and besieged by these mood disorders, whereby they can often dominate and affect the person more than the symptoms of AS itself (Atwood, 2007).

Co morbidity is defined as the co-occurrence of two or more disorders in the same individual (Matson & Nebel-Schwalm, 2007). A co morbid condition is a second order diagnosis which exhibits symptoms that are different from the primary diagnosis or condition (Mannion & Leader, 2013). ASD is associated with a high possibility of co morbid psychological disorders. Symptoms resulting from co-existing conditions often present to be just as debilitating as the core characteristics of AS and are equally in need of appropriate medical intervention and treatment (Williams, Matson, Beighley, Rieske & Adams, 2014).

This piece of work reviews the current literature on the prevalence of seven of the main coexisting conditions that can be present in individuals with AS, namely: Obsessive Compulsive Disorder (OCD), Bipolar Depression (BD), mood disorders, anxiety, Attention Deficit, Hyperactivity Disorder (ADHD), epilepsy and oppositional defiant disorder (ODD). Followed by an exploration into the use of pharmacological treatment of such conditions and the outcome of a number of clinical trials examining the utilization of medication for the mental health disorders associated with AS.
Psychiatric co morbidity in Asperger Syndrome

The first systematic study on co morbid neuropsychiatric disorders in AS was conducted by Ghaziuddin, Weidmer-Mikhai, & Ghazziudin (1998) which included 35 individuals with AS; it was found that 65% of individuals within this sample were affected by one or more additional psychiatric disorder(s). A more recent study by Mukaddes & Fateh (2010) showed that the occurrence of additional psychiatric disorders was 9% and the majority of participants (70%) had more than one additional psychiatric diagnosis. Matson & Goldin (2013) revealed that the bulk of the research on co morbid psychopathology is on ADHD, general psychopathology and anxiety. In light of this, the co morbidity of such conditions in AS is an area of research that requires further exploration and analysis.

Comorbid Neuropsychiatric Disorders of AS

Obsessive compulsive disorder

Mukaddes & Fateh (2010) recorded that the diagnosis of OCD in persons with AS is a controversial issue. Since compulsive ritualistic behaviour is a characteristic and an integral element of AS, OCD is often left undetected. In other words, OCD can often be masked by the core symptoms of AS and therefore can often be difficult to unpack and diagnose as a distinct co-existing condition, that requires separate consideration. Thomsen (1999) disclosed that although research examining the correlation between OCD and AS is scarce, it often emerges in people with AS. With this said, Mukaddes & Attwood (2006) estimated that 25% of individuals diagnosed with AS also have OCD. Lynn (2007) also records OCD as one of the prevalent coexisting conditions of AS.

Research conducted by Ruta, Mugno, D’Arrigo, Vitello & Mazzone (2010) examined the occurrence of obsessive compulsive symptoms in children with AS compared with typically developing children with OCD. From this study, it was found that the AS group had significantly higher incidences of compulsive hoarding, repeating and ordering compared to typically developing children. Baron-Cohen et al. (2000) recorded that the correlation between ASD’s and OCD as well as other psychiatric symptoms including anxiety seems to be further supported by the observations that some brain regions (i.e. amygdale) play a crucial role in ASD’s, in relation to abnormal fears, compulsive behaviours and heightened anxiety. In addition to these more frequently co-occurring conditions in AS, co morbid eating
disorder and body dysmorphia may also be present in young individuals with OCD (Philips, Menard, Fay & Weisberg, 2005).

**Depression and mood disorders**

It has become evident from research data that while depression can arise and present itself across the entire spectrum of autism, individuals who are at the higher functioning end of the spectrum tend to be particularly affected (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000; Whitehouse, Durkin, Jacquet, & Ziatas 2009). A study carried out by Tantam (1991) revealed that depression is most certainly common in individuals with AS, with about 1 in 15 people with AS experiencing the related symptoms. Furthermore, research carried out by Ghaziuddin, Ghaziuddin & Greden, (2002); Mayes, Calhoun, Murray, Ahuja, & Smith, (2011) indicated that reports of depression are common among persons at the more advanced end of the ASD spectrum (individuals with HFA/AS) with incidence rates between 25% and 34%.

Findings from literature data compiled by Kim, Szatmari, Bryson, Streiner, & Wilson (2000) revealed that depression was more evident in children aged 10-12 years with HFA/AS than in the entire population of children in the same age group. Findings from a study conducted by Cassidy et al. (2014) showed that two-thirds (66%) of adults with AS had considered suicide and over a third (35%) had planned or attempted suicide throughout their life span. In adults with AS and a history of depression and mood disorders, suicidal thoughts and behaviours were significantly more common. According to Professor Baron-Cohen (2014), “Adults with Asperger Syndrome often suffer with secondary depression due to social isolation, loneliness, social exclusion, lack of community services, under-achievement, and unemployment. Their depression and risk of suicide are preventable with the appropriate support”.

Mazzone et al. (2013) relayed that although the correlation with depression is one of the most common co-morbidities found in persons with AS, some individuals also exhibit mood swing that may be associated with bipolar disorders. For example, Munesue et al. (2008) have shown that in 44 consecutive outpatients with HFA, 36.4% were diagnosed with mood disorders and of these individuals, bipolar disorder accounted for 75% of cases. In a
study by Hofvander et al. (2009) the most prevalent co morbid condition was mood disorder, with 53% of individuals having a diagnosis. A study conducted by Lugnegard, Hallerback and Gillberg (2011) on 26 men and 28 women with a diagnosis of AS found that in a sample of young adults with AS, 70% had experienced at least one episode of major depression.

**Anxiety**

Research conducted by Tantam and Prestwood (1999) stated that individuals with HFA or AS are particularly susceptible to mental health problems such as anxiety disorders, especially in late adolescence towards early adulthood. It was found by Muris, Steerneman, Merclekbck, Holdrinet & Meesters (1998) that 84.1% of children with pervasive developmental disorders met the diagnostic criteria for at least one anxiety condition (panic disorder, general anxiety disorder, avoidant disorder, phobia). Individuals with AS are often more susceptible to anxiety disorders as a result of the social demands and pressures made upon them within society. Prevalence studies indicate that around 13.6% of children with AS suffer from clinically relevant anxiety (Kim, Szatmari, Bryson, Streiner, & Wilson, 2000) and up to 45% of adolescents with AS have significant problems with generalised anxiety, social anxiety or specific phobias (Green et al. 2000). A study conducted by Hofvander et al. (2009) revealed that 50% of the participants had a diagnosis of some form of anxiety. In addition, a study was conducted by Lugnegard, Hallerback and Gillberg (2011) on 26 men and 28 women with a diagnosis of AS. It was found that in a sample of young adults with AS, approximately 50% had an anxiety disorder.

**Attention Deficit/ Hyperactivity Disorder (ADHD)**

Dr. Ghaziuddin (2005) stated that having a neuro-developmental disorder such as AS can automatically increase the likelihood of a co morbid ADD or ADHD diagnosis. Research conducted by Gargaro, Rinehart, Bradshaw, Tonge, & Shepard (2011) revealed that the frequency of ADHD in those with ASD has ranged from 14% to 78%. Hofvander et al. (2009) examined psychiatric co morbidity and compared the incidence of psychiatric disorders among three groups; persons with Autistic Disorder, those with AS and those with pervasive development disorder- not otherwise specified (PDD-NOS). Findings revealed that
43% of these individuals were diagnosed with ADHD. The prevalence of ADHD comorbidity in AS has received considerable attention and has been subject to much debate. The diagnostic and comorbid debate is ongoing between clinical opinion, research practice and theoretical models surrounding the comorbidity of the relevant and frequent occurrence of these disorders in AS (Gargaro, Rinehart, Bradshaw, Tonge & Shepard, 2011).

**Epilepsy**

Mouridsen, Rich & Isager (2013) asserted that one of the widely recognised central nervous system (CNS) associations with ASD’s is epilepsy. The possibility of epilepsy can vary depending on the subtype within the autism spectrum. The lowest incidence rates (4%) have been documented in AS (Cederlund and Gillberg, 2004) and the highest have been documented in childhood disintegrative disorder (77%) (Mouridsen et al. 1999) and Rett’s syndrome (94%) (Steffenburg, Hagberg, & Hagberg, 2001).

**Oppositional defiant disorder**

The prevalence of the behavioural disorder (ODD) in children in the general population usually decreases with age or the condition often changes into conduct disorder, but based on the results from a study by Mattila et al. (2010), the signs and symptoms of ODD seem to be permanent during childhood in individuals with AS/HFA. In accordance with the findings of co-occurrence of ODD and anxiety disorders from this study, Mattila et al. (2010) revealed that ODD may also be a behavioural manifestation of anxiety in individuals with AS/HFA.

Overall, it is evident that individuals with AS often present with one or more comorbid conditions that require medical intervention. Findings from a study conducted by Farrell, Waters, Millner & Ollendick (2012) revealed that 86% of young people presented with a secondary psychiatric disorder and 74% presented with a tertiary psychiatric condition. Kutscher (2005) denoted that ASD’s such as AS tend to be highly comorbid, with ADHD, depression, anxiety, OCD and sensory integration problems can often become the main cause
of concern. These clinical characteristics therefore bestow the rationale for the utilization of psychotropic medication (psychopharmacology) in persons with AS (Tsai, 2007).

Medication treatment in AS

It is evident that individuals with AS can be affected by a diverse range of mental health problems, predominantly anxiety and depression but also ADHD, OCD and mood swings. Grandin (2000) stated that there is no psychiatric pharmacological treatment for autism, but there are many psychiatric medications utilized for treating the specific symptoms often found in autism and AS, such as aggression, self-injury, anxiety, depression, OCD, and ADHD. These types of medications usually function by altering the level of neurotransmitters in the brain. In order to achieve effective medication treatment in persons with AS, it is essential for individuals and professionals to learn and train themselves about the key principles of psycho-pharmacology, the work-ups for utilization of various medications, the indications and contraindications of the specific medication and the effective outcomes of medication along with prevention, recognition, and management of medication-induced side effects (Tsai, 2007).

It was highlighted by Mazzone, Ruta, Reale (2012) that proper identification and diagnosis of psychiatric co morbidities in AS/HFA is imperative for the pharmacological treatment of these individuals. Tsai (2007) declared that pre-treatment assessment is also vital for establishing the individual’s baseline physical, psychological, behavioural, and cognitive status before first line medication treatment, as well as for examining both the effectiveness of and any problematic side effects to the medication utilized. Matson & Williams (2014) however concluded that treatment research is limited relative to explaining and assessing co morbidity among persons with ASD. Mazzone, Ruta, Reale (2012) further relayed that to date, very few studies have examined the effectiveness of pharmacological treatment in AS/HFA. The majority of clinical trials conducted on AS/HFA have concentrated on drug treatment strategies geared towards the behavioural symptoms (motor hyperactivity and inattention, interfering stereotypical and repetitive behaviour, self- injury, aggression), whereas only few controlled studies investigated and tested the pharmacological drugs geared towards the particular psychiatric disorders most commonly associated in co morbidity with autistic symptoms in HFA/AS.
Effectiveness of pharmacological treatment in AS

To date, peer reviewed journals and studies on the medication treatment of AS and co-morbid neuropsychiatric disorders are lacking. Matson and Goldin (2013) argued that this may be the case because the view of co-morbid conditions among individuals with ASD is a relatively new concept. For example, the DSM-IV documents that ASD and ADHD cannot be diagnosed simultaneously. The fact that a dual diagnosis cannot be made is an interesting matter since the incidence of these two conditions co-occurring is relatively high (Tureck, Matson, May, Davis & Whiting, 2013).

Woodbury-Smith and Volkmar (2009) stated that although there are no clinical trials determining the efficacy of antidepressants in persons with AS, because of its effectiveness in the general population, they stated that there should be no hesitation to believe that this medication would be less efficacious in AS.

Vannucchi et al. (2014) asserted that in treating the co-morbidity of Bipolar Disorder (BD) in AS, mood stabilizers and antipsychotics, particularly second generation drugs (SGA) with 5-HT2a antagonism, have been shown to be useful in keeping psychotic and behavioural symptoms under control and improving social withdrawal in persons with AS. Research data from clinical trials have been examined to evaluate the anti-manic short-term (8 weeks) effectiveness of specific SGA (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole) in young people with co-morbid ASD and BD. 69% of BD individuals and 65% of BD+ ASD individuals showed an improvement of at least 30% at the Young Mania Rating Scale (Y-MRS), and 47% of BD individuals compared to 44% of BD+ ASD had an improvement of at least 50% at the same measure (Joshi et al. 2012).

A few studies involving children and adults with ASD have revealed efficacy for Fluoxetine (Ghaziuddin, Tsai & Ghaziuddin, 1991), Citalopram (Namerow, Thomas, Bostic, Prince & Monuteaux, 2003) and Mirtazapine (Posey, Guenin, Kohn, Swiezy & McDougle, 2001). A study by Frazier, Doyle, Chiu, & Coyle (2002) reported on a 13 year old boy with a diagnosis of AS and bipolar disorder. This young boy had a history of aggression and unsafe behaviours. After treatment for many years with a mixture of psychotropic medications which proved no effect, the researchers came to light and found that a combination of 1 mg twice a day of oral clonazepam, 2,100 mg per day of lithium, and 3 mg per day of risperidone led to a noticeable decline in his problematic behavioural symptoms. Continuous assessment
of the outcome of this treatment plan later revealed that his mood stabilized and his aggressive, extremely compulsive and disruptive behaviours disappeared.

Given the biochemical underpinning frequently involved with depression, medication often plays a crucial role in treatment. Kutscher (2005) revealed that a half to two thirds of children experience a significant beneficial effect from Selective Serotonin Reuptake Inhibitors (SSRI). The medication of choice for most mood disorders in the general population are SSRI anti-depressants, although medical research tends to relay that this mode of treatment may not be efficacious (Williams, Wheeler, Silove & Hazell, 2010). While other SSRIs are often specifically used in the treatment process, only Prozac has U.S. Food and Drug Administration (FDA) approval for use in children with depression.

Tsai (2007) reported that it is still unclear whether ultracyclical bipolar mood disorder is a part of AS or if it should be regarded as a different type of mood disorder. Tsai (2007) conveyed that bipolar mood disorder does not seem to respond well to the mood stabilizers such as Depakote, Zyprexa (danzapine), Risperdal and Tegretol (carbamazepine). It has also been stated that in treating the comorbidity of Bipolar Disorder in AS, the utilization of most antidepressants can actually worsen the clinical condition. Antidepressants such as SSRI have induced mania in some individuals with AS (Damore, 1998) and have also caused their aggressive behaviour to worsen. Before SSRI is utilized in the treatment plan for depressive or obsessive-compulsive symptoms of AS, the presence of co morbid BD or bipolar awareness should be excluded. A study conducted by Raja & Azzoni (2008) revealed that risperidone low-doses associated with anticonvulsants have demonstrated a good efficacy in the therapy of BD-AS co morbidity.

Evidence is present showing that certain pharmacological treatments may prove to be beneficial and effective for people with AS affected by anxiety. A study carried out by Santosh and Barid (1999) revealed that individuals may respond well to buspirone, propranolol or clonazepam. On the other hand, Carpenter (2001) specified that St. Johns Wort, benzodiazepines and SSRI antidepressants to be more effective. Farmer, Thurm & Grant (2013) stated that due to the high prevalence rate of epilepsy found in individuals with ASD, anticonvulsants are commonly used in this population base.

Kutscher (2005) expressed that many children and young adolescence with ADHD benefit from medication. Durrand (2014) stated that pharmacological intervention is often
used when children with ASD exhibit symptoms of ADHD. It is reported that approximately one third of school-going children with ASD receive stimulant medications for symptoms of ADHD (Pringle, Colpe, Blumberg, Kogan, 2012), although stimulants seem to be effective for only a minority of individuals with ASD and often have intolerable medication-induced side effects (Research Units on Pediatric Psychopharmacology Autism Network, 2005). In a case study conducted by Gutkovich, Carlson, Carlson, Coffey & Wieland (2007) an individual (L.) was treated somewhat successfully with a combination of risperidone elixir titrated up to 1.5mg per day (receiving this treatment for the next 4 years) and guanfacine 1 mg twice a day for inattention, hyperactivity and tics. Targeted combined pharmacotherapy with lithium, risperidone and guanfacine normalised L’s behaviour and enhanced his school functioning. Psychostimulants such as methylphenidate, and selective noradrenergic reuptake inhibitors, such as atomoxetine, are utilized to treat ADHD. In AS children and adolescents there is evidence for the efficacy of methylphenidate (Research Units on Pediatric Psychopharmacology Autism Network, 2005).

While some atypical antipsychotics (such as risperidone and aripiprazole) have been explored by many researchers, others (such as olanzapine, quetiapine and ziprasidone) have had limited data in relation to effectiveness and side effects (Malone, Delaney, Hyman & Cater, 2007). It has been reported by Kemner et al. (2002) that olanzapine shows very little effect on certain ASD symptoms and individuals can experience water retention and weight gain and can also be burdened by side effects such as sedation. Also, Sung et al. (2014) reported that there have been no recent published studies on the utilization of asenapine, sertinode, iloperidone, or amisulpride. Politte & Mcdougle (2014) reported that among second generation antipsychotics (SGA’s) risperidone and aripiprazole have been extensively studied and represent the only ones with a Food and Drug Administration (FDA) signal for the treatment of irritability in ASD children.

A study conducted by King et al. (2009) examining the suggested relationship between repetitive behaviour in ASD’s and OCD’s, investigated the response to citalopram therapy in children with ASD and the outcome revealed no difference in the improvement’s rate of repetitive behaviour between the citalopram-treated group and the placebo group. This implies that the compulsive behaviours present in ASD’s may have a qualitative different nature than those of an OCD.
Tsai (2007) successfully used Luvox in treating OCD in children with AS. Research by Sasayama et al. (2009) revealed the effectiveness of another medication, paroxetine in improving obsessive compulsive behaviour. In a study by Bernhardt, Walsh & Posey (2011) memantine was administered to a 15 year old boy at 2.5mg/ day, gradually titrated to 10mg/ day to stabilize the individuals OCD symptoms which over the next few months improved significantly. The young boy expressed having less desire to perform rituals, and experienced fewer intrusive, disturbing thoughts. This study showed a significant improvement with memantine in an individual with co morbid OCD and AS. On the other hand, mood stabilizers, such as lamotrigine and levetiracetam have been shown to be ineffective for repetitive behaviour and social symptoms (Belsito et al. 2001, Wasserman et al. 2006).

**Conclusion**

Williams, Matson, Beighley, Rieske & Adams (2014) reported that as researchers and clinicians adopt the new DSM-5 criteria, it is crucial to examine the implications of these changes and to assure that children whose needs warrant clinical intervention are freely able to access services, whatever their diagnosis may be. Furthermore, Mannion & Leader (2013) stated that it is imperative that there is an understanding of the different types of co morbid disorders that affect those with ASD among both professionals and researchers.

At present, there are no scales particularly constructed to evaluate psychiatric co morbidity in individuals with ASD’s, and the research data that explored co morbid disorders in AS/HFA either referred to the DSM-IV diagnostic criteria, or attempted to adjust the scales used for the general population, and that clearly has several drawbacks and limitations (Mazzone, Ruta, Reale, 2012). Posey et al. (2007) purported that it should be possible to diagnose AS/HFA and ADHD and/or OCD concurrently in order to target the most appropriate treatment. In order to improve outcomes of individuals with AS, it is crucial that public awareness of the condition is increased so that diagnosis can be rendered earlier and the most suitable supports can be put in place (Barnhill, 2007).

It is evident throughout this literature review that a number of studies have investigated some of the associated co morbid conditions that are often found in individuals with AS. Although to date, there is still limited research into the co morbid conditions that can manifest and affect people with AS, the types of medication sought through clinical intervention and the outcomes from the use of medication. It is pivotal that more longitudinal
studies on AS/HFA are carried out in order to comprehend the lifetime history of the disorder and the role of co morbid disorders (Mazzone, Ruta, Reale, 2012).

This research study is being undertaken by ASPIRE- Asperger Syndrome Association of Ireland and focuses on individuals with AS who have one or more co-existing conditions, the medications they are prescribed, as well as the negative/ positive, outcomes and experience of treatments. Although the core symptoms of AS need to be differentiated from the presence of any comorbid conditions and vice versa; treatment for AS and comorbidities should be holistically considered and analysed through the same lens when treatment, policies and prescriptions are being developed and evaluated. Therefore, simultaneous diagnosis of AS and comorbid conditions is essential to appropriately treat an individual who is affected from AS and a comorbid condition(s), as these disorders may interplay with each other. This research aims to raise awareness around these issues along with contributing to laying a foundation for further research into this area of development. Research into this area is pivotal to raise awareness around the existence of co morbid conditions in AS.
References


