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Understanding the Importance of the Evaluation and Treatment of Elevated Androgens in Autism Spectrum Disorder

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1. Introduction

Autism spectrum disorder (ASD) is a prevalent, life-long, neurodevelopmental disorder diagnosed in more than 1% of children in the United States (the most recent estimate exceeds one in 68 children) with strong gender basis towards males (one in 42 boys) relative to females (one in 189 girls) [1]. In addition to the diagnostic impairments specified in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for ASD in socialization, restricted, repetitive patterns of behavior, interests, or activities, and communication, which must be present in the early developmental period, many individuals diagnosed with an ASD frequently have co-morbid aggression and severe irritability, hyperactivity, and repetitive behaviors, which can become a major source of additional distress and can interfere with functioning [2]. Similarly, others have observed the occurrence of co-morbid conditions among individuals diagnosed with an ASD as follows: hyperactivity (67%), sensory processing problems (85%), anxiety/fear (74%), behavioral problems (89%), and obsessive-compulsive behaviors (92%) [3]. These investigators described that behavioral problems and obsessive-compulsive behaviors were reported to be the most serious and problematic. In addition, investigators described that some individuals diagnosed with an ASD show significant deterioration in symptoms about the time of puberty [4]. Among the symptoms that worsened according to these investigators were disruptive behavior, destructiveness, restlessness, and partial loss of acquired social and academic skills.

In considering the aforementioned facts, it was previously hypothesized that male hormones (androgens) may play a critically important role in the clinical presentation of individuals diagnosed with an ASD and that reduction of androgens in individuals diagnosed with an

ASD would result in a significant amelioration of their clinical symptoms [5]. The purpose of this critical review is to examine evidence supporting the role of androgens in mediating ASD traits/symptoms, elevated androgens among individuals diagnosed with an ASD, and the observed important role for anti-androgen medications in treatment of ASD traits/symptoms.

2. Evidence for a correlation between elevated androgens and ASD traits/symptoms

Investigators have systematically evaluated measurements of androgens and their relationship with the clinical symptoms or traits defining or observed in individuals diagnosed with an ASD [6, 7]. Fetal testosterone levels were observed to be significantly inversely related to eye contact, quality of social relationships, vocabulary size, and empathy among typically developing children. By contrast, fetal testosterone levels were observed to significantly positively correlate with autistic traits, restricted interests, and systemizing behaviors.

It was also determined on a psychological testing basis that there were significant differences among individuals diagnosed with an ASD in comparison to neurotypical males and females [6, 7]. The tests revealed that autism quotient (AQ), systemizing quotient (SQ), child autism spectrum test (CAST), embedded figures test, intuitive physics test, social responsiveness scale, quantitative checklist for autism in toddlers (Q-CHAT) scores revealed a pattern of ASDs > males > females. By contrast, empathy quotient (EQ), faux pas test, friendship and relationship questionnaire (FQ), reading the mind in the eyes, and social stories questionnaire (SSQ) scores revealed a pattern of females > males > ASDs.

Other investigators examined brain structure for evidence of an extreme male brain among individuals diagnosed with an ASD in comparison to neurotypical males and females [6, 7]. A pattern of extreme male brain structure with ASD > males > females for total brain volume and amygdala size was observed. By contrast, it was observed that the brain size was females > males > ASD for the perisylvian language areas, left > right asymmetry in planum temporale, and lateral fronto-parietal cortex. Furthermore, brain function patterns revealed females > males > ASD for default mode network connectivity, embedded figures functional magnetic resonance imaging (fMRI), and reading the mind in the eyes task fMRI.

Still other investigators examined the relationship between various diseases known to be associated with elevated androgen levels and ASD traits and symptoms [6, 7]. For example, individuals diagnosed with congenital adrenal hyperplasia (CAH) were found to have increased problem behaviors and increases in AQ scores relative to unaffected controls. It was even observed that some individuals diagnosed with DNA-confirmed CAH mutations and associated clinical and laboratory findings had a concurrent diagnosis of an ASD. As another example, individuals diagnosed with polycystic ovarian syndrome (PCOS) were observed to have significantly increased AQ scores, significantly impaired communication, socialization, and attention relative to unaffected controls. Finally, investigators examined bio-physiological and cognitive differences in children diagnosed with premature adrenarche (with elevated blood androgen levels) in comparison to on-time adrenarche [8]. Children diagnosed with

premature adrenarche in comparison to on-time adrenarche had significantly increased problem behaviors and attention problems, as well as significantly decreased skills in socialization, information processing, language/communication.

Other investigators have more specifically examined the direct relationship between hormonal treatment status and ASD traits/symptoms by examining various groups of transsexual individuals [9] and among individuals injected with testosterone in a double-blind study [10]. It was observed among various groups of transsexual individuals that compared ASD traits/symptoms using AQ scores derived from five groups: (1) $n = 61$ transmen (female-to-male transsexual individuals); (2) $n = 198$ transwomen (male-to-female transsexual individuals); (3) $n = 76$ typical males; (4) $n = 98$ typical females; and (5) $n = 125$ individuals diagnosed with an ASD [9]. Higher AQ scores were seen in transmen than in typical females, typical males, or trans women, but transmen had lower SQ scores than those individuals diagnosed with an ASD. Transmen displayed ASD-like symptoms/traits and were more comfortable socializing with male peers than female peers. Thus androgen treatment in transmen correlated directly with development of ASD symptoms/traits. Transmen had a higher mean AQ than typical females, typical males and transwomen, but lower than individuals diagnosed with an ASD. Transmen have more ASD traits/symptoms and may have had difficulty socializing with female peers and thus found it easier to identify with male peer groups. The importance of these findings being that direct hormonal treatment with androgen therapy in transmen directly correlated with their development of ASD traits/symptoms. It was also observed, among individuals injected with testosterone in a double-blind study, that these individuals manifested a significant increase in ASD traits/symptoms with impairment in their cognitive ability to infer emotions, intentions, feelings, and other mental states from observing the eye region of another's face [10].

3. Evidence for the effect of elevated androgens in ASD

Investigators have undertaken extensive evaluation of various measurements of elevated androgens in individuals diagnosed with an ASD. They described, among individuals diagnosed with an ASD, significantly increased frequency of genetic changes in multiple genes involved in sex steroid synthesis, transport, and/or metabolism, testosterone-related medical conditions (e.g., polycystic ovarian syndrome, breast and ovarian cancers, acne, etc.), and testosterone-related characteristics (e.g., tomboyism, etc.) [6, 7]. It was also reported that individuals diagnosed with an ASD had significant alterations in the timing of puberty (boys diagnosed with an ASD were observed to enter "male" puberty earlier, while girls diagnosed with an ASD were observed to enter "female" puberty later). Elevated androgen levels and significantly lower second to fourth digit ratios in comparison to neurotypical controls (a known marker of elevated fetal testosterone) [6, 7].

Investigators recently measured fetal steroidogenic activity in amniotic fluid samples for individuals diagnosed with an ASD in comparison to neurotypical controls. Amniotic fluid samples taken from individuals subsequently diagnosed with an ASD in comparison to neurotypical controls revealed significant elevations in androgen levels [11].

Investigators previously described evaluating blood androgen levels among a large cohort of individuals diagnosed with an ASD using routine laboratory testing from the Laboratory Corporation of American (LabCorp) [12]. It was observed that individuals diagnosed with an ASD were observed to have significant increases in their blood levels of testosterone, free testosterone, dehydroepiandrosterone (DHEA), and androstenedione relative to laboratory provided reference ranges. Overall, it was observed among the various blood androgen attributes examined, that over 80% of the individuals diagnosed with an ASD examined were found to have at least one of the blood androgen attributes examined that exceeded the age- and sex-specific reference ranges provided by the laboratory.

Subsequently, other investigators evaluated the potential role of androgens among individuals diagnosed with an ASD in comparison to neurotypical controls by examining salivary levels of hormones among children from 3-4 years-old and 7-9 years-old [13]. These investigators observed significantly higher salivary concentrations of androgens among individuals diagnosed with an ASD relative to controls, and the anomalies were prominent in older male children diagnosed with an ASD. Among the specific types of androgens observed to be increased among individuals diagnosed with an ASD in comparison to neurotypical controls were androstenediol, DHEA, and androsterone, which, the investigators concluded were indicative of precocious adrenarche and predictive of early puberty. These investigators also commented that some of the androgens observed were significantly increased among the individuals diagnosed with an ASD relative to the neurotypical controls are known to neuroactive and modulate GABA, glutamate, and opioid neurotransmission with the potential consequence of affecting brain development and function. They may also contribute to ASD-associated pathobiology and symptoms such as elevated anxiety, sleep disturbances, sensory deficit, and stereotypic behaviors.

Similarly, other investigators examined hyperandrogenemia in male children and adolescents diagnosed with an ASD in comparison to neurotypical controls and in relation to ASD severity by assessing serum androgen levels [14]. These investigators observed that androgen levels were significantly higher among individuals diagnosed with an ASD in comparison to neurotypical controls, and the elevations were observed to significantly correlate with ASD severity. Overall, it was observed among individuals diagnosed with an ASD that 36.66% had high serum free testosterone, 30% had high DHEA, 40% had high androstenedione, and 26.66% showed elevation of all androgen levels in comparison to neurotypical controls. These investigators concluded that hyperandrogenemia is prevalent among individuals diagnosed with an ASD, correlate with ASD severity, and studies should explore the use of anti-androgen therapy to treat such patients.

4. Treatment with anti-androgen medications in ASD

It was originally hypothesized that given the significant correlation between androgen levels and ASD symptoms/traits that administration of anti-androgen medications to individuals diagnosed with an ASD would result in significant clinical improvements [5]. More recently

other investigators extended this previous hypothesis by suggesting that circulating hormone levels and the administration of testosterone and other hormones were found to predict behavior in individuals, but the effect was suggested to be one of "activation" or "fine-tuning" earlier organization of the brain [15].

Among the most-well studied anti-androgen medications are gonadotropin-releasing hormone (GnRH) analogues. GnRH analogues are synthetic peptide drugs modeled after human hypothalamic GnRH, and are designed to interact with the GnRH receptor and modify the release of pituitary gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) for therapeutic purposes, and over a period of time will lower the release of FSH and LH from the pituitary leading to reversible suppression of androgen release [16].

The use of GnRH analogues in various animal model systems has been observed to significantly improve many ASD symptoms/traits, and the improvements observed were comparable to those for commonly used psychiatric medications for these conditions [7]. For example, investigators studied the effects of GnRH agonists and antagonists on anxiety and social behaviors in rats [17]. These investigators observed GnRH agonists significantly reduced anxiety and increased social behaviors in the rats, and the overall effects were comparable to those observed with diazepam. Other investigators examined the effects of GnRH agonists on obsessive compulsive behaviors in mice. In one study it was observed that a GnRH agonist was able to significantly reduce marble-burying behaviors, a model system for obsessive-compulsive behaviors, comparable to that observed with fluoxetine administration [18], and in another it was observed that a GnRH agonist was able to significantly reduce marble-burying behaviors comparable to that observed with ritanserin administration [19]. Finally, investigators observed that GnRH agonist therapy significantly improved hyperactivity behaviors in mice [20].

In addition to studies of animal model systems demonstrating the improvement of ASD symptoms/traits by GnRH analogues, a number of investigators have observed similar phenomena in human populations. For example, investigators examined the acute gonadal suppression effects of GnRH antagonists on sexual and behaviors in a case-series of men [21]. It was observed the treatment resulted in significant reduction in outward-direct aggression in all of the treated men with some also experiencing reductions in anxiety and sexual desire. Other investigators reported on the use of a GnRH analogue to treat obsessive-compulsive disorder in a clinical trial [22]. During the course of the 48 week clinical trial, it was observed that GnRH analogue therapy was effective in significantly reducing the severity of the symptoms of obsessive-compulsive disorder. Another investigator described the use of a GnRH analogue as a means to treat problems behaviors in men suffering from dementia [23]. It was observed that within 4 weeks of the start of therapy, verbal and physical aggression had decreased; activity disturbances such as agitation, pacing, and restlessness were markedly reduced; and a significant reduction in disruptive sexual behaviors was observed.

Investigators have reported on the successful use of GnRH analogues in the treatment of sexual problem behaviors/symptoms in individuals diagnosed with an ASD over several decades. For example, investigators described that administration of an GnRH analogue to an individual diagnosed with an ASD and sexual behavior resulted in significant suppression of the

patient's sexual behaviors [24]. Similarly, other investigators described the use of GnRH analogues in the treatment of individuals diagnosed with an ASD and central precocious puberty [25]. These investigators described that many individuals diagnosed with an ASD tend to have early sexual maturation, and they described a case-series of patients with precocious puberty ranging from 6 years and 9 months-old to 9 years and 6 months-old. Treatment with a GnRH analogue to help alleviate their symptoms of precocious puberty, especially given that these symptoms were not well-tolerated in the context of the individual's ASD diagnoses. These investigators concluded that treatment of sexual precocity should be considered among individuals diagnosed with an ASD not only based upon their bone age maturation and growth, but also their mental maturation.

Finally, investigators described the successful use of the GnRH analogue, leuprolide acetate, in the treatment of ASD traits/symptoms in a clinical trial of consecutive individuals diagnosed with an ASD with laboratory findings showing elevated androgen levels [26]. Each patient was clinically studied at base line and at the end of the study, to evaluate hyperandrogenemia behavior/symptoms including secondary sexual changes, facial and body hair, early growth spurt and aggressive behaviors. A clinical examination was undertaken for each individual to evaluate clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors at baseline and at the end of the study period for each child. Autism Treatment Evaluation Checklist (ATEC) evaluations were completed by the child's parents prior to beginning the protocol and at the end of the study period for each child. The children received 15 mg of leuprolide acetate depot by intramuscular injection every 28 days. This dose was supplemented with a daily subcutaneous injection of leuprolide acetate so that each child received a total initial starting doses of 50 ug of leuprolide acetate/kilogram of body weight-daily. The children were monitored, and increased subcutaneous doses of leuprolide acetate or oral anti-androgen medication were administered to those children who exhibited persistent laboratory/clinical signs of elevated androgen as clinically indicated. The participants were enrolled in the study for a minimum of 2 months and a maximum of 7 months. Each child underwent laboratory testing at baseline and again after approximately 3 of treatment. Treated children were observed to significantly improve from a median baseline score of 87 (70th percentile of autism severity) to a median score of 63 (40-49th percentile of autism severity) by the completion of the study. Significant improvements among treated children when evaluating baseline measurements in comparison to those obtained at the end of the study period, were observed in the specific areas of sociability, cognitive awareness, and behavior. Additionally, trial participants having independent assessments by school evaluators showed significant improvements in general school skills mastered and significant improvements in the frequency and severity of disruptive/oppositional behavior at the end of the treatment period relative to baseline, despite the fact that the evaluators were unaware of the child's participation in the trial.

Comparison of clinical evaluation at baseline with evaluation at the trials conclusion showed significant reductions in hyperandrogenemia evidenced in clinical symptoms and the associated behaviors (early secondary sexual changes, early growth spurt, body and facial hair, and aggressive behaviors). A significant decrease in serum testosterone levels was demonstrated

by laboratory testing, and the treatment protocol did not significant adversely affect kidney, thyroid or liver function tests.

Since their study employed therapeutic agents designed to lower androgen levels, and significant decreases in androgen levels were observed, the researchers concluded the treatment protocol studied presented a novel method to significantly reduce autistic-like behaviors. Further, the study reported that significant autistic behavior improvements (i.e., improvements in hyperactivity and attention, better sleep patterns, and increased socialization) occurred within days of the treatment with leuprolide acetate. Finally, the study concluded that leuprolide acetate significantly ameliorated clinical behaviors/systems of hyperandrogenemia including aggressive behaviors,, early secondary sexual changes,, body and facial hair, and early growth spurt among children diagnosed with an ASD.

Other investigators reported that the administration of leuprolide acetate therapy to nearly 200 individuals diagnosed with an ASD [12] resulted in significantly lowered androgen levels very significant overall clinical improvements in sensory/cognitive awareness, socialization, and health/physical/behavior skills. Leuprolide acetate treatment resulted in significant clinical ameliorations in aggression, self injury, abnormal sexual behaviors, hyperactivity/impulsivity, stereotypy, and/or irritability behaviors in many individuals diagnosed with an ASD. Minimal adverse clinical effects to the therapy were seen, and there were with few non-responders.

Children were administered an intramuscular injection of 15 mg leuprolide acetate depot every 28 days and supplemented with daily, subcutaneously injected leuprolide acetate, so that children were started on a dose of 50 µg of leuprolide acetate/kilogram bodyweight/day. Children were monitored as successive doses of leuprolide acetate were administered for persistent clinical/laboratory signs of increased androgens, and subjects were treated with additional subcutaneous injections of leuprolide acetate dosing and/or an oral anti-androgen medicine as clinically necessary.

Children examined in the study were on the therapy for a minimum of 2 months and a maximum of 7 months. Laboratory testing was conducted on each child at baseline and at approximately 3 months of treatment. Among the children treated in the clinical trial, there was a significant overall improvement from the 70th percentile of severity (median baseline score = 87) at baseline to the 40-49th percentile of severity (median end of study period score = 63) at the end of the study. In the specific areas of sociability, cognitive awareness, and behavior, there were significant improvements among treated children when evaluating baseline measurements in comparison to those obtained at the end of the study period. Additionally, for specific subjects participating in the clinical trial having independent assessments by school evaluators, who were not aware of the treatment status of the child, there were significant improvements in general school skills mastered and significant improvements in the frequency and severity of disruptive/oppositional behavior at the end of the treatment period relative to baseline.

When comparing the clinical examinations undertaken for each child at baseline and at the end of the study period, significant reductions in clinical symptoms and the associated

behaviors of hyperandrogenemia (such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors) were noted. Laboratory testing revealed a significant decrease in serum testosterone levels. It was observed that the treatment protocol did not significantly adversely affect kidney, thyroid or liver function tests.

As a result, the investigators concluded, since their study employed therapeutic agents that were designed to lower androgen levels, and significant decreases in androgen levels were observed, the treatment protocol presented a novel method for helping to significantly reduce autistic-like behaviors. Furthermore, the investigators reported that in some of the children examined, significant autistic behavior improvements (i.e., better sleep patterns, improvements in attention and hyperactivity, and increased socialization) occurred within days of the administration of leuprolide acetate. Finally, the investigators concluded that leuprolide acetate administration significantly helped to ameliorate clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors that may be observed among some children diagnosed with an ASD.

Subsequently, other investigators described their clinical experience following the administration of leuprolide acetate therapy to nearly 200 individuals diagnosed with an ASD [10]. Leuprolide acetate administration significantly lowered androgen levels and resulted in very significant overall clinical improvements in socialization, sensory/cognitive awareness, and health/physical/behavior skills, with few non-responders and minimal adverse clinical effects to the therapy. Leuprolide acetate administration also resulted in significant quantitative clinical ameliorations in hyperactivity/impulsivity, stereotypy, aggression, self injury, abnormal sexual behaviors, and/or irritability behaviors in many individuals diagnosed with an ASD.

Recently, investigators have purposed clinical guidelines for the evaluation and treatment of androgen dysfunction in individuals diagnosed with an ASD [7, 27]. It is important when considering medicines such as leuprolide acetate for the treatment of individuals diagnosed with an ASD, to consider that such therapy is not intended to deprive the individual of their sexuality nor alter their normal developmental trajectory. Instead, the initiation of such therapy is designed to regularize a process that was proceeding in an abnormal fashion and producing adverse effects. Thus, the use of anti-androgen medicines, such as leuprolide acetate, can safely improve the health of the individual diagnosed with an ASD by reducing in the frequency and intensity of their ASD traits/symptoms

In considering the in-use safety of GnRH analogues in the treatment of individuals diagnosed with an ASD, they have been on the market for many years, and many individuals have received GnRH analogues for many years to treat conditions such as prostate cancer, female reproductive problems, and premature puberty without serious adverse effects [7]. Studies of individuals receiving GnRH-analogue therapy for many years in the treatment of premature puberty reported that GnRH analogue administration was not associated with long-term reproductive dysfunction. The patients had normal menarche normal ovarian function etc. No impaired physical development was observed. The patients had normal body composition, normal body mass index, normal bone mineral density, etc. No reduction in the secretion of

sex hormones in men and women was observed [7]. In 2009 the American Academy of Pediatrics issued a consensus statement describing that GnRH analogues are generally well tolerated in adolescents and children. Systemic complaints such as hot flashes or headaches occur occasionally but are usually short-term and do not interfere with therapy [28].

In previous long-term follow-up of individuals receiving GnRH-analogue therapy in the treatment of premature puberty for many years, the studies reported that GnRH analogue administration was not associated with long-term reproductive dysfunction (normal ovarian function, normal menarche, etc.); impaired physical development (normal body mass index, normal body composition, normal bone mineral density, etc.); or reduced secretion of sex hormones in women and men [7]. The American Academy of Pediatrics in 2009 issued a consensus statement describing that GnRH analogues are generally well tolerated in children and adolescents, and systemic complaints such as headaches or hot flashes occur occasionally but are usually short-term and do not interfere with therapy [28].

Furthermore, when considering the safety profile of GnRH analogues among individuals diagnosed with an ASD, it is important to evaluate them in the context of currently used psychotropic medicines. For example, risperidone is currently approved by the US Food and Drug Administration (FDA) for the treatment of individuals diagnosed with an ASD. Investigators recently reported on the long-term treatment effects of risperidone on prolactin levels, sexual side-effects, and bone mineral density in pubertal boys diagnosed with an ASD [29-31]. The individuals diagnosed an ASD examined were physically healthy 10 to 20 year-old males chronically treated with risperidone for an average of 52 months (range 16 to 126 months). It was observed when comparing individuals chronically treated with risperidone in comparison to individuals not treated with any antipsychotic medicine, hyperprolactinemia was present in 47% of the chronically treated individuals in comparison to only 2% of the individuals not treated with any antipsychotic medicine. In addition, gynecomastia and sexual dysfunction were present in 43% and 14% of the individuals chronically treated with risperidone in comparison to 21% and 0% of individuals not treated with any antipsychotic medicine. Individuals chronically treated with antipsychotic medicines who developed hyperprolactinemia were compared to individuals not treated with any antipsychotic medicine and had no hyperprolactinemia. The patients treated with antipsychotic medicines had significantly lower lumbar spine bone mineral density scores, higher percentage of body fat, and a lower biochemical bone marker carboxyterminal cross-linking telopeptide of bone collagen. Finally, it was observed among individuals chronically treated with antipsychotic medicines who developed hyperprolactinemia in comparison to individuals not treated with any antipsychotic medicine who did not have hyperprolactinemia had significantly lower testosterone levels.

5. Conclusion

The present critical review provides evidence for hyperandrogenism as a significant feature among ASD. Further, many studies have shown a significant correlation between the traits/

symptoms of individuals diagnosed with an ASD and hyperandrogenism. Finally, the present critical review presents data from animal models and human clinical trials demonstrating that medication with anti-androgens significantly improve certain traits/symptoms exhibited by individuals diagnosed with an ASD.

The present critical review provides evidence for hyperandrogenism as a significant feature among individuals diagnosed with an ASD. Further, many investigations have revealed a significant correlation between the traits/symptoms of individuals diagnosed with an ASD and hyperandrogenism. Finally, the present critical review presents data from animal models and human clinical trials demonstrating that anti-androgen medications have the ability to significantly improve certain traits/symptoms exhibited by individuals diagnosed with an ASD.

In light of the high prevalence of individuals diagnosed with an ASD and the paucity of safe and effective medical treatments to help these individuals, anti-androgen therapy should be considered as it is an effective and relatively safe means to significantly help improve the adverse traits/symptoms exhibited by individuals diagnosed with an ASD. By directly targeting a traits/symptoms and/or biomedical indicators when elevated beyond the normal ranges, this therapy controls difficult traits/symptoms associated with high androgens such as self injurious behaviors and aggression, and, thus, contributes to the quality of the individual's life and the normalcy of the individual's home life.

It is recommended that all individuals diagnosed with an ASD should be screened for elevated androgens and elevated androgen-associated traits/symptoms as part of a standard initial clinical assessment. In addition, these same type of blood and clinical traits/symptoms should be assessed within the affected individual's family, so as to produce not only treatment options for the individual diagnosed with an ASD but also an understanding of why these conditions occur and who may be at risk. Finally, for those appropriate individuals diagnosed with an ASD, anti-androgen treatment should be offered.

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