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Behavioral and Psychiatric Phenotypes in 22q11.2 Deletion Syndrome

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Abstract

22q11.2DS is a chromosomal microdeletion that affects approximately 40–50 genes, and impacts various organs and systems throughout the body. Detection is typically achieved by fluorescence in-situ hybridization following diagnosis of one of the major features of the deletion or via chromosomal microarray or non-invasive prenatal testing. The physical phenotype can include congenital heart defects, palatal and pharyngeal anomalies, hypocalcemia/hypoparathyroidism, skeletal abnormalities, and cranial/brain anomalies, although prevalence rates of all of these features are variable. Cognitive function is impaired to some degree in most individuals, with prevalence rates of greater than 90% for motor/speech delays and learning disabilities. Attention, executive function, working memory, visual spatial abilities, motor skills, and social cognition/social skills are affected. The deletion is also associated with an increased risk for behavioral disorders and psychiatric illness. The early onset of psychiatric symptoms common to 22q11.2DS disrupts the development and quality of life of individuals with the syndrome, and is also a potential risk factor for later development of a psychotic disorder. This review discusses prevalence, phenotypic features, and management of psychiatric disorders commonly diagnosed in children and adolescents with 22q11.2DS, including autism spectrum disorders, attention deficit/hyperactivity disorder, anxiety disorders, mood disorders, and schizophrenia/psychotic disorders. Guidelines for the clinical assessment and management of psychiatric disorders in youth with this syndrome are provided, as are treatment guidelines for the use of psychiatric medications.

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Conflicts of Interest

The authors have no conflicts of interest to declare

Introduction

This review of 22q11.2 deletion syndrome (22q11.2DS) is intended to provide guidance for treatment and management, with the intended audience of developmental behavioral pediatricians, child psychiatrists, and possibly geneticists and primary care providers. 22q11.2DS is a relatively common multiple anomaly syndrome caused by a deletion of the q11.2 band of one copy of chromosome 22, affecting roughly 40–50 genes. 22q11.2DS has an estimated population prevalence of 1:4000 – 1:6000 live births,[1] although a recent publication cites a frequency as low as 1/992[2]. Although the phenotype varies considerably, multiple body systems are often affected and typically include characteristic facial features, cardiac defects, palatal anomalies, immune deficiency, cognitive impairments, and psychiatric disorders. Throughout the history of the syndrome, 22q11.2DS has been identified by several clinical descriptors, including velo-cardio-facial syndrome (VCFS), conotruncal anomalies face syndrome, and DiGeorge syndrome. However, in 1992, it was discovered that all of these clinical disorders shared the same genetic microdeletion.[3] Since then, there has been a general movement toward referring to the syndrome as 22q11.2DS as it is the most descriptive name.

The phenotype for 22q11.2DS includes physical, metabolic, endocrine, and behavioral features.[4] Although many body systems can be affected, no one anomaly occurs in 100% of cases. Bassett, et al.[5] reported prevalence rates for multisystem features present in 22q11.2DS, and those rates are used here. The physical phenotype can include congenital heart defects (50%–75% prevalence), palatal and pharyngeal anomalies (75% prevalence), vascular anomalies, facial dysmorphism (prevalence >90%) and hypocalcemia/hypoparathyroidism (60% prevalence).

Arguably, the most commonly (82–100%) occurring symptoms, are behavioral and developmental issues. [6] A wide range of general cognitive abilities (mild intellectual disability to average IQ) has been observed with mean full-scale IQ (FSIQ) scores typically in the borderline range,[7] with approximately 50% of individuals with scores less than 70, and performance IQ (PIQ) slightly lower than verbal IQ.[6,8,9] It is important to note, however, that this IQ pattern is not present across all individuals with 22q11.2DS. In studies of intellectual functioning throughout development in 22q11.2DS, cognitive abilities were found to be inversely associated with age, with both VIQ and PIQ scores showing a cross-sectional decline with age.[10,11] Vorstman, et al.,[12] using a large, pooled cross-sectional dataset from an international research consortium, reported that individuals with 22q11.2DS between 8 and 24 years of age showed an average 7-point decline in FSIQ, driven by an average 9-point decline in VIQ and average 5.1-point decline in PIQ. Attention abilities are impaired,[9,13] as are deficits in executive function, shifting attention, working memory, and reactive response inhibition.[14–19] Impairments in visuospatial perception and visuospatial memory are also common in 22q11.2DS,[6,20–23] and are often thought to be the underlying reason for mathematical deficits.[24] Relative deficits include spatial working memory[21] and the endogenous cueing function of visual attention (in younger children)[22].

Academically, children with 22q11.2DS typically fare better in their early school years and many do not begin to experience impairments until the later elementary school years (3–4th

grade), when the focus begins to shift from concrete to more abstract thinking. Receptive language is typically stronger in the preschool years, and although general language problems become apparent in the early school years, reading, spelling, and rote verbal memory remain in the low- to high-average range, with verbal memory being consistently stronger than visuo-spatial memory.[25] Reading comprehension abilities also often lag behind reading decoding and phonological processing abilities, [6,20,26,27] and receptive language abilities are generally stronger than expressive language abilities, although the opposite pattern has been observed as well.[28] Written language abilities are often impaired as well, possibly related in part to graphomotor difficulties and/or expressive language difficulties.[6,25] Accordingly, although the term of non-verbal learning disability has been applied at times to children with 22q11.2DS, the language based learning difficulties noted above render this label somewhat misleading, and often inaccurate.[29]

Motor deficits have also been reported in children with 22q11.2DS, including early hypotonia, coordination/balance deficits, delayed walking[30] and, during adolescence, problems with motor speed.[6] Although fine motor difficulties are also present, generally gross motor skills are more markedly impaired.[6] In a study of 56 children (mean age = 9.65 years, *SD* = 1.93), those with 22q11.2DS performed significantly worse than age- and IQ-matched controls on tasks of manual dexterity, visual perception, and motor coordination, suggesting that visual-perceptual and visuo-motor integration skills are specifically affected.[31] Additionally, axial stability is somewhat impaired in those with 22q11.2DS.[32]

Behavioral Challenges

The behavioral phenotype of children with 22q11.2DS has been studied extensively. Children with 22q11.2DS have been described as overactive, impulsive, emotionally labile, shy/withdrawn, and/or disinhibited.[6,33,34] Indeed, the temperament of children and adolescents with 22q11.2DS have also been assessed via parent report. Relative to unaffected siblings and typical controls, children with 22q11.2DS have a generally more difficult temperament.[35] Specifically, children with the syndrome were rated as being less regular in their daily habits (e.g. eating at the same time each day, etc.), more rigid and less able to respond flexibly to changes in the environment, less able to focus/sustain attention, less cheerful/pleasant and less likely to stay with an activity for a long time. However, in a study based on parent and teacher reports, Swillen[36] found that school-aged children with 22q11.2DS generally exhibited the similar behaviors as age-, sex-, and IQ-matched children with idiopathic developmental delays. The exceptions were that children with 22q11.2DS demonstrated more social withdrawal, and non-syndromal children with developmental delays demonstrated more aggressive behaviors. In general, many of the behaviors exhibited by children with 22q11.2DS (e.g., overactivity, impulsivity, poor organizational skills) are also common in children with idiopathic developmental delays.[37] Therefore, it is difficult to differentiate behaviors that are primarily psychiatric conditions stemming from the deletion from behaviors that are due to other risk factors associated with developmental delays and cognitive/intellectual deficits.

Social Cognition/Social Skills

Social functioning in 22q11.2DS appears to be affected as well. Youth with 22q11.2DS tend to have internalized-type social problems (social withdrawal); however, many also tend to have problems with attention/concentration, which can lead to disinhibition and impulsivity.[7] A developmental progression has been documented, moving from more of an externalizing profile (e.g., impulsive, oppositional) at a younger age, to an internalizing profile in adolescence (e.g., withdrawn, exhibiting somatic complaints, anxiety, depression).[6] It has been hypothesized that the social withdrawal that is common in youth with 22q11.2DS may be partly due to their difficulty communicating with others, to velophyarngeal dysfunction, or to neuropsychological limitations that can make interaction with others difficult.[7] It remains unclear whether the social impairments are primary or secondary symptoms of the deletion.

Impairments in social cognition are generally seen as a central aspect of idiopathic schizophrenia. As such, Jalbrzikowski[38] investigated social cognitive abilities in 22q11.2DS as predictors of positive and negative symptoms of psychosis. Youth with 22q11.2DS were impaired on tasks of Theory of Mind (ToM; the ability to understand what another person is thinking or feeling) and processing speed. ToM emerged as the best indicator of positive symptoms of psychosis, and processing speed was the best indicator of negative symptoms of psychosis. Additionally, a cross-sectional study[39] including classic social-cognitive, false-belief and mentalizing tasks, and social-perceptual face processing tasks, found that younger children with 22q11.2DS exhibited social-perceptual deficits, including matching faces on the basis of identity, emotion, facial speech, and gaze. Performance was positively associated with age, language abilities, and social competence, and negatively associated with emotional problems.[39] Moreover, in a study of mental state attributions, Ho, et al.[40] found that individuals with 22q11.2DS (aged 6–25 years) had decreased intentionality and appropriateness scores for ToM, but not for random scenes. ToM was significantly correlated with scores on the Social Responsiveness Scale. Finally, the authors of a study that investigated social skills and associated psychopathology in 22q11.2DS suggested that treating behavioral/emotional disorders (e.g., ADHD, anxiety, internalizing symptoms) may help improve social skills, as deficits in social skills were found to be more closely related to emotional/behavioral issues than delays in neurocognition.[41]

Psychiatric Phenotype

The early onset of psychiatric symptoms common to 22q11.2DS disrupts the development and quality of life of individuals with the syndrome, and is also a potential risk factor for later development of a psychotic disorder. Accordingly, in the following section, we discuss the prevalence, phenotypic features and management of common psychiatric disorders in 22q11.2DS. Note that these disorders include many of the behavioral and cognitive problems described above. Likewise, many comorbidities in 22q11.2DS are similar to those with idiopathic conditions (e.g., schizophrenia, anxiety). Several years ago, Bassett and colleagues[5] outlined the multisystem features of 22q11.2DS and recommended general surveillance and management approaches for all common medical and psychiatric comorbidities. Developmental pediatricians are particularly likely to provide care for those

patients with 22q11.2DS that also have psychiatric disorders [42]. Thus, we focus on standard surveillance and management approaches for 22q11.2DS-affected youth with psychiatric disorders, and provide guidance for issues that may be somewhat specific to the 22q11.2DS population. Nonetheless, most of these comorbidities can be managed by non-22q specialists with consideration for medical (cardiac, endocrine, etc.) conditions that might require lower dosing or more frequent monitoring. We have organized our review by the typical age of onset, beginning with conditions that characteristically are diagnosed in childhood. We have also provided a table that summarizes prevalence rates of each disorder in 22q11.2DS, and information about assessment and evidence-based treatments (See Table 1).

Although the psychiatric phenotype of 22q11.2DS has been the focus of numerous research studies in recent years, and despite the identification of many important aspects, there remained inconsistencies regarding prevalence rates of particular psychiatric disorders. Most studies have been conducted on relatively small samples, and rarely addressed issues of comorbidity or sex differences. To address these concerns, The International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome gathered research groups from North America, Europe, Australia, and the Middle East to collaborate and share knowledge and data. This collaboration has resulted in a comprehensive report of the prevalence of psychiatric disorders across the lifespan, patterns of comorbidity across diagnostic categories, and sex distributions of psychiatric disorders in 1,402 individuals with 22q11.2DS.[43] Age categories include children (aged 6–12 years), adolescents (aged 13–17 years), emerging adults (aged 18–25 years), young adults (aged 26–35 years), and mature adults (aged 36 years and over). Prevalence rates listed below (and detailed in Table 1) are taken from the Consortium report by Schneider and colleagues.

Autism Spectrum Disorders

The Consortium report found that the prevalence of autism spectrum disorders (ASD; including autistic disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified) was lowest among children (12.77%), highest among adolescents (26.54%), then dropped off again in emerging adulthood (16.11%). Unlike the broader ASD population, gender differences in ASD prevalence rates in 22q11.2DS have not been observed.[43] A 2006 study found autism or pervasive developmental disorder not otherwise specified (PDD-NOS) in 50% of a sample of 60 participants with 22q11.2DS aged 9–18 years.[44] Interestingly, 33.3% of the remainder of the sample scored above cutoff levels on three domains of autistic symptomatology. Similarly, in a 2007 study of 41 children and adolescents with 22q11.2DS (aged 6.5 – 15.8 years), Antshel et al.[45] found that 20% of their sample met strictly defined criteria for autism while over 40% met criteria for an autism spectrum disorder. When compared to children youth with 22q11.2DS and no ASD diagnosis, those with both 22q11.2DS and ASD were more likely to have comorbid ADHD and specific phobias, as well as more symptoms of mania.[45] It has consistently been reported that idiopathic ASD often co-occurs with other psychiatric disorders.[44,45] Thus, ASD with and without 22q11.2DS is often accompanied by co-occurring psychiatric diagnoses. Further investigation is required to determine the extent to which the psychiatric comorbidity found in 22q11.2DS is affected by the presence of ASD, or vice versa. In

addition, future studies should investigate the high prevalence of ASD and the degree to which ASD accounts for the deficits in social functioning typically seen in 22q11.2DS.

The *American Academy of Child and Adolescent Psychiatry* (AACAP) has several recommendations for screening and assessment of ASD.[46] Note that all of the screening and diagnostic tools that we describe here and below should be administered and interpreted either by a multi-disciplinary team or in consultation with a mental health professional (e.g. child psychiatrist or child psychologist). Assessment instruments for ASD include: (a) using a screening instrument such as the Modified Checklist for Autism in Toddlers (M-CHAT)[47] for toddlers and the Autism Screening Questionnaire[48] for older children; (b) conducting a diagnostic assessment including both the Autism Diagnostic Interview – Revised (ADI-R) [49] and the Autism Diagnostic Observation Schedule – 2nd edition (ADOS-2)[50] for those children who screen positive for possible ASD; (c) administering psychological assessment, including cognitive and adaptive measures, which can be helpful for treatment planning for most youth with 22q11.2DS, yet especially those with comorbid ASD. AACAP recommendations for treatment of youth with ASD include behavioral interventions based upon Applied Behavioral Analysis (ABA) principles with an explicit focus on generalization, pharmacotherapy for comorbid conditions such as anxiety or ADHD and programs designed to enhance social reciprocity and communication skills.[46]

The diagnosis of ASD in 22q11.2DS can be difficult to make given the phenotypic overlap between the two conditions.[51] For example, similar to what has been reported in ASD,[52] children and adolescents with 22q11.2DS spend less fixation time on the eyes and more time fixating on the mouth during emotion processing tasks.[53] However, previous research has suggested that several differences may exist between those with 22q11.2DS and 22q11.2DS + ASD, as well as between those with 22q11.2DS and idiopathic ASD. Children with 22q11.2DS + ASD have less joint attention with others, lower levels of make believe play, and higher levels of restricted and repetitive behaviors than those with 22q11.2DS alone.[54] Likewise, as noted above, children with 22q11.2DS + ASD have higher levels of psychiatric comorbidity than those with 22q11.2DS alone.[45] Compared to individuals with idiopathic ASD, children with 22q11.2DS display more socioemotional reciprocity.[54] Accordingly, it has been suggested that an accurate diagnosis of ASD in 22q11.2DS depends on the integration of multiple sources of information[51] to enable the clinician to differentiate between the phenotype that is common to most children with 22q11.2DS and ASD per se.[54] Likewise, the current guidelines for making an ASD diagnosis include the use of both the Autism Diagnostic Interview – Revised edition (ADI-R)[49] and the Autism Diagnostic Observation Schedule - Second Edition (ADOS-2).[50] Very few 22q11.2DS studies have utilized both of these assessments in making an ASD diagnosis. Thus, future research should consider prevalence rates of ASD in 22q11.2DS using the current assessment guidelines. Finally, it should be noted that, to the best of our knowledge, no studies have investigated treating ASD in individuals with 22q11.2DS.

Attention Deficit/Hyperactivity Disorder

Schneider and colleagues reported that, among those with 22q11.2DS, prevalence rates for ADHD were highest among children, and higher in adolescence than adulthood. Of the 200

(out of 263) individuals with 22q11.2DS for whom the ADHD subtype was available, 63% met the diagnostic criteria for the inattentive subtype, 6.5% for the hyperactive-impulsive subtype, and 30.5% for the combined subtype. ADHD was more prevalent in males (60.87%) than females (39.13)[43]. For many reasons, ADHD is more difficult to diagnose in adults, which may help explain the decrease in diagnoses in adults with 22q11.2DS. Additionally, ADHD declines as a function of age in non-22q11.2DS populations as well. This is thought to be due to the natural progression of the condition (hyperactivity wanes with age), as well as the developmental insensitivity of the ADHD symptoms that are outlined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV). A distinct profile of ADHD symptoms and psychiatric comorbidity has been reported for children with 22q11.2DS and ADHD, compared to children with idiopathic ADHD.[55] Antshel et al.[55] studied children and adolescents with ADHD, stratified by the presence or absence of 22q11.2DS (*n* = 34 22q11.2DS + ADHD; *n* = 280 ADHD). Controls were children without ADHD, both with (*n* = 68) and without 22q11.2DS (*n* = 242). No age differences existed between the four groups and the overall mean age for the entire sample was 11.1 years (SD = 2.4 years). Results indicated that the specific inattentive symptoms with which youth with 22q11.2DS demonstrate include: (a) failure to give close attention to details or makes careless mistakes in schoolwork, (b) does not seem to listen when spoken to directly, (c) failure to follow through on instructions and to finish schoolwork, chores (not due to oppositional behavior or failure to understand instructions) and (d) avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework). Conversely, children with idiopathic ADHD are more likely to have difficulty sustaining attention in tasks or play activities. For the hyperactive/impulsive symptoms, children with 22q11.2DS + ADHD are more likely than children with idiopathic ADHD to fidget with hands/feet or squirm in his/her seat. Conversely, children with idiopathic ADHD are more likely to (a) run about or climb excessively in situations in which it is inappropriate, (b) have difficulty playing or engaging in leisure activities quietly, (c) be “on the go” or act as if “driven by a motor” and (d) blurt out answers before questions have been completed. Youth with 22q11.2DS + ADHD are rated by parents as having higher levels of social, somatic, thought and internalizing symptoms than those with idiopathic ADHD. Moreover, children with 22q11.2DS and ADHD are more likely to be diagnosed with the inattentive subtype of ADHD than are children with idiopathic ADHD. Additionally, children with 22q11.2DS and ADHD are more likely to exhibit thought and social problems, as rated by their parents; children with idiopathic ADHD, however, were more likely to be diagnosed with comorbid major depression and disruptive behavior disorders than are those with 22q11.2DS and ADHD.

AACAP practice parameters for screening and assessment of ADHD include: (a) screens for ADHD symptoms using a standardized rating scale like the Conner’s Rating Scales – 3rd edition[56] or Vanderbilt ADHD Scales;[57] (b) for those that screen positive, thorough assessments that include clinical interviews with the child and parent, information about the child’s functioning and comorbid psychiatric disorders, and a review of medical and social histories; and (c) psychological and neuropsychological assessments to inform treatment planning for those with ADHD.[58] Evidence based interventions for ADHD include pharmacotherapy, behavioral parent training, contingency management approaches used in

the school setting, comprehensive school-based treatment programs and intensive summer treatment programs.

To our knowledge, there are no data that have been published on ADHD non-pharmacological treatment outcomes in the 22q11.2DS population. Two studies have considered methylphenidate treatment outcomes in 22q11.2DS (see Psychiatric Medication Treatment section below).

Anxiety Disorders

Anxiety disorders are the most common psychiatric disorder in 22q11.2DS. In the Consortium sample, Schneider et al.[43] found that prevalence rates for anxiety, including separation anxiety, specific phobias, social phobias, panic disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), generalized anxiety disorder (GAD), and anxiety disorder not otherwise specified, decreased significantly from childhood (35.63%) to mature adulthood (27.56%) with the lowest rates being seen in emerging adulthood (24.07%) and young adulthood (24.83%). The subcategories with the highest prevalence rates are specific phobias (21.94% in childhood), social phobias (10.34% in childhood), OCD (5.52% in childhood), and GAD (8.28% in childhood). Panic disorder is the only subcategory that showed a significant increase in prevalence over time, from 1.20% in childhood, to 14.41% in mature adulthood. Anxiety disorders were more prevalent in females than males, across the entire group (57.22%), but this difference was only significant in adults, not in children or adolescents.[43] The nature of OCD in 22q11.2DS appears to be similar to children who have idiopathic OCD.[59] In a study of OCD in 22q11.2DS, Gothelf and colleagues assessed 43 subjects aged 6 – 40 years. They found the mean age of OCD diagnosis was 13.1 years, with the first signs appearing, on average, 2.4 years before acquiring the diagnosis. Common comorbidities for children with 22q11.2DS and OCD were the same for children with idiopathic OCD: other anxiety disorders, disruptive disorders, and ADHD. Gothelf et al. suggested that the presence of 22q11.2DS predisposes one to develop OCD, based on the finding that obsessive-compulsive symptoms were commonly found in participants with the deletion who did not meet the diagnostic criteria for OCD. Repetitive questions, fear of contamination with cleaning compulsions, hoarding, and aggressive and somatic obsessions were the most common symptoms, which are consistent with idiopathic childhood-onset OCD, with the exception of aggressive obsessions.[59]

Screening and assessment guidelines that have been published by AACAP[60] include (a) screening for anxiety symptoms using the Multidimensional Anxiety Scale for Children - 2nd Edition (MASC-2)[61] or the Screen for Child Anxiety Related Emotional Disorders (SCARED)[62] and (b) for those youth that screen positive, conduct a formal evaluation to determine which anxiety disorder may be present, the level of associated functional impairments and possible differential diagnoses or comorbid conditions. Evidence based interventions for anxiety disorders include cognitive behavioral therapy (CBT), family interventions and SSRIs.[60] CBT typically includes psychoeducation with child and parents, relaxation training, cognitive restructuring, exposure methods (imaginal and in vivo) and relapse prevention.

Anxiety disorders are very common in the 22q11.2DS population. Yet to our knowledge, there are no data that have been published on treatment outcomes of anxiety disorders in the 22q11.2DS population. Nonetheless, given the data suggesting that modified CBT can be effective in anxious youth with autism spectrum disorder[63,64] and parent-child CBT can be effective for children as young as age 4,[65] modified CBT approaches should be investigated in the 22q11.2DS population.

Mood Disorders

Mood disorders are common among individuals with 22q11.2DS. Prevalence rates for major depressive disorder (MDD) increase with age from childhood (2.19%), adolescence (8.96%), emerging adulthood (10.84%), young adulthood (12%) and peak in mature adulthood at 15.75%. Dysthymia is most prevalent in emerging adults (5%), as is mood disorder not otherwise specified (2.17%). Bipolar disorder/(hypo)manic episodes increase with age, being most prevalent in mature adulthood (3.94%). Unipolar disorders (MDD and dysthymia) are overrepresented in females (61.18%), but the sex differences were only significant in adults, not in children or adolescents.[43] Interestingly, an increase in depressive episodes has been reported early in adolescence (age 12–15),[66,67] which may be considered unique to 22q11.2DS, as depressive disorders in the general population have been found to appear later in adulthood, with a median age of onset for mood disorders of 30 years.[68] Indeed, in a sample of 172 individuals with 22q11.2DS, the incidence of depression was found to be the highest, at 18.5%, among young adults (18–24 years of age).[10] Fabbro and colleagues[66] observed that the trajectory of prevalence of depression corresponds to the timing of certain developmental milestones that typically require increased levels of autonomy/independence and social integration, and so may be driven by feelings of low self-esteem or inadequacy as the effects of the syndrome are becoming more impairing. Fabbro and colleagues found that deficits in everyday adaptive skills and social functioning (as reported by parents) were positively correlated with an increase in frequency and severity of depressive and anxious symptoms (as reported by the participants) in a study of 74 children and adolescents (age range: 6–18 years) with 22q11.2DS.[66]

AACAP screening and assessment guidelines for depressive disorders[69] include (a) establishing a confidential relationship with the child or adolescent while maintaining collaborative relationships with adults in the child's life; (b) using screening questions with checklists developed from DSM symptoms; and (c) for those youth that screen positive, a thorough evaluation should ensue and include assessment for the presence of harm to self or others, the presence of ongoing or past exposure to negative events and the environment in which the depression is developing. Evidence based interventions for depressive disorders include CBT, interpersonal psychotherapy, and antidepressant medication.[69,70]

Similar to anxiety disorders, depressive disorders are common in the 22q11.2DS population, especially in adolescents and adults. Nonetheless, there are no data that have been published on treatment outcomes of depressive disorders in the 22q11.2DS population.

Schizophrenia/Psychotic Disorders

In the Consortium sample, Schneider et al. found prevalence rates for schizophrenia spectrum disorders (including schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, and delusional disorder) significantly increase across age groups among individuals with 22q11.2DS, with children at 1.97%, adolescents at 10.12%, emerging adults at 23.53%, young adults at 41.33% and mature adults at 41.73%. There was no sex difference in the prevalence of psychotic disorders.[43] Similarly, Green and colleagues[10] observed (in a two-site sample of 172 individuals with 22q11.2DS, aged 5 – 54 years) a gradual increase in the prevalence of psychotic disorders, from none in the children's age group, to 3.8% in adolescents, to 22.2% in young adults aged 18 to 24 years, and ultimately reaching 30% in adulthood (above the age of 24 years). Participants with comorbid 22q11.2DS and a psychotic disorder had significantly lower Verbal IQ scores than the participants with the deletion but without psychosis.

Individuals with the deletion are in the third-highest risk category for developing schizophrenia, behind only the monozygotic twin of an individual with schizophrenia, and the offspring of two parents with schizophrenia. Thus, it is quite possible that some of the 22q11.2DS behaviors observed in childhood (e.g., social withdrawal) are actually prodromal features of psychosis.[43] Schizophrenia in 22q11.2DS has been found to be indistinguishable from the idiopathic schizophrenia phenotype on many variables, including age at onset, lifetime and cross-sectional core features, global functioning, severity of anxiety-depression symptoms, and cognitive symptoms.[71] One study investigated subthreshold prodromal symptoms in a sample of 157 individuals with 22q11.2DS. Using the Structured Interview for Prodromal Syndromes (SIPS) adapted for this population, the authors found subthreshold prodromal symptoms to be common, with limited ideational richness, trouble with focus and attention, avolition, and impaired tolerance of normal stress especially common. Perceptual abnormalities/hallucinations, unusual thought content/delusional ideas, and suspiciousness/persecutory ideas were the most commonly found positive psychotic symptoms.[72] Moreover, in the large consortium study on IQ noted above, Vorstman and colleagues found that in the 12% of the sample that developed a psychotic illness, the decline was markedly steeper for FSIQ and both subscales, but was most pronounced for VIQ. These findings indicate that early cognitive decline in 22q11.2DS is a risk factor for the development of psychotic illness.[11,12] Additional predictors of either psychotic symptoms or psychosis that have been reported (based on longitudinal studies) include baseline externalizing symptoms, social dysfunction, anxiety disorders, executive dysfunction, and lower full-scale IQ scores.[73–75] Further systematic investigation of prodromal psychotic symptoms in children and adolescents with 22q11.2DS, including childhood screening for prodromal symptoms, appears warranted.

AACAP screening and assessment guidelines for schizophrenia include (a) asking screening questions for psychosis in a developmentally sensitive way (e.g., "Do you hear voices talking to you when no one is there?") including direct assessment of the youth as well as obtaining information from parents and family members and (b) those who screen positive should have a comprehensive evaluation that uses DSM-5 diagnostic criteria, the same

criteria that are utilized for adults, and carefully considered for comorbid conditions. Treatment of schizophrenia in children and adolescents should include antipsychotic medication and include baseline and follow-up monitoring of symptoms and side effects.[76] Psychoeducation, cognitive remediation, and combined psychoeducation and cognitive remediation have been demonstrated to be effective for adolescents with schizophrenia.[77,78] Prodromal symptoms of schizophrenia are common in youth with 22q11.2DS. To our knowledge, there are no data that have been published on non-pharmacological treatment outcomes of schizophrenia or prodromal symptoms in the 22q11.2DS child/adolescent population. Two very recent studies have been published on pharmacological treatments for adults with 22q11.2DS and psychosis. Clozapine was found to be as effective for individuals with 22q11.2DS and schizophrenia as it was for those with idiopathic schizophrenia (no deletion), but the 22q11.2DS group was disproportionately affected by rare serious side effects, specifically seizures.[79] Further, clozapine and quetiapine were both found to be effective in a group of adults with 22q11.2DS and treatment-resistant psychosis and were made more tolerable by the addition of the mood-stabilizing anticonvulsant valproic acid.[80]

Treatment Guidelines For Psychiatric Medication Use In Children With 22q11.2DS

Very few studies have evaluated the effectiveness and safety of psychotropic medication in children with 22q11.2DS. Two methylphenidate studies, one an open-label study, and the other a randomized control trial, concluded that methylphenidate is efficacious and well tolerated in children with 22q11.2DS and comorbid ADHD.[81,82] Although methylphenidate was determined to be a safe medication to prescribe, adverse effects of clinically significant increase in heart rate and blood pressure were noted in a few cases. A comprehensive cardiovascular evaluation was recommended for children with 22q11.2DS prior to and during treatment with methylphenidate.

Only one other study[83] has examined the effectiveness and safety of psychotropic medications in children with 22q11.2DS and psychiatric comorbidity. The results of this retrospective study concluded that antipsychotic and antidepressant medication may be effective in treating children who have psychotic or mood or anxiety diagnoses. The antipsychotic (risperidone, olanzapine, quetiapine, clozapine, clotiapine, and fluphenazine) and the antidepressant (escitalopram, fluoxetine, paroxetine, setraline, venlafaxine) medications were generally well tolerated. The authors concluded that antipsychotics should be considered for children with 22q11.2DS who have comorbid schizophrenia spectrum disorders, and antidepressants should be considered for children who have comorbid depressive and/or anxiety disorders. Although in need of replication with much larger samples, the results of this small, retrospective study concluded that antipsychotic and antidepressant medication may be effective in treating children who have psychotic, or mood or anxiety, diagnoses. More rigorous metabolic and cardiovascular measures were recommended for future studies to provide further evidence of the safety of these medications.

Despite the paucity of research regarding the effectiveness of psychiatric medication treatment in children with 22q11.2DS, these medications are commonly prescribed for

individuals with 22q11.2DS and comorbid psychiatric conditions. The same standards of care that apply to use of these medications in children should be considered when prescribing them for children with 22q11.2DS. FDA approved psychiatric medications for children should be considered as the first drug of choice. The following medications have been approved for use in children: stimulants, atomoxetine, alpha-2 agonists for ADHD; escitalopram and fluoxetine for depression, fluoxetine, sertraline, and fluvoxamine for OCD; risperidone, aripiprazole, olanzapine, and haloperidol for psychotic symptoms and mania; risperidone, aripiprazole for irritability associated with autism; and lithium for mania.

Because children with 22q11.2DS have comorbid medical conditions, certain additional precautions should be considered when prescribing psychotropic medications. Many children with 22q11.2DS have cardiovascular anomalies and may therefore be more vulnerable to psychotropic medications that can have adverse cardiac effects (atomoxetine, alpha agonists, stimulants, and antipsychotics). Using caution by prescribing initial low doses of medication and closely monitoring for cardiac arrhythmias are recommended.

In summary, ASD, ADHD, anxiety disorders, depressive disorders and schizophrenia are frequently diagnosed in children and adolescents with 22q11.2DS. Developmental pediatricians that clinically manage youth with 22q11.2DS should screen for and, when appropriate, assess for the presence of these psychiatric disorders. While some 22q11.2DS phenotypic features may make screening for diagnosing the psychiatric condition more challenging, developmental pediatricians are encouraged to follow standard AACAP guidelines for screening and diagnosing DSM-5 disorders. Very little data have been published on 22q11.2DS medication treatments and no data have been published on 22q11.2DS psychosocial interventions. These significant gaps represent clear areas of need for future 22q11.2DS research. Without these specific 22q11.2DS treatment outcome studies, developmental pediatricians are encouraged to recommend evidence based interventions (see Table 1) to families with 22q11.2DS yet recognize that these interventions may need to be tailored for use with youth with 22q11.2DS.

Conclusions and Future Directions

There has been a substantial amount of research done in the last two decades regarding the effects of 22q11.2DS on developmental, cognitive and psychiatric functioning. At least some of the focus is now beginning to turn to the development of effective treatment approaches. Cognitive remediation (CR), especially when coupled with other psychiatric rehabilitation treatment modalities, has been shown to be effective in improving attention, memory, problem solving ability, and global cognition in adults with schizophrenia.[84,85] CR is now being investigated in individuals with 22q11.2DS. Harrell et al.[86] found that a short-term CR intervention program was feasible in a small sample of children with 22q11.2DS, who showed improvement in a cognitive composite score and simple processing speed. Mariano and colleagues[87] found significant post-treatment improvements with small to medium effect-sizes in working memory, shifting attention, and cognitive flexibility utilizing a longer-term (average treatment time of approximately 8 months), remotely-administered, computer-based cognitive training program. The study provided support for the feasibility of a relatively intense training schedule with individuals with 22q11.2DS, and

incorporated an analysis of fidelity of the coach's interventions in the strategy-based/drill-and-practice approach. As a new avenue of exploration, CR in 22q11.2DS remains an exciting area of research, with many new studies being conducted. Future studies will likely include no-coach control groups to investigate the effects of the presence of a coach, longer duration and more intense training schedules to maximize the potential for improvements to generalize to other areas of functioning and to persist over time, and include social cognitive skills training as well.

There is much interest in 22q11.2DS in the field of neuropsychiatric research, and many avenues of discovery to pursue. The link between 22q11.2DS and schizophrenia continues to be investigated, with many neuroanatomic studies underway, to help delineate the structural and functional differences seen in schizophrenia. Discoveries continue to be made at the genetic level as well, as more candidate genes are being identified and their roles in the phenotype being delineated. Social cognition is also an area in which there is much interest in developing evidence-based interventions. Pharmacological interventions are being investigated as well, especially in terms of their effectiveness in combination with traditional therapy and cognitive remediation in schizophrenia. Interventions provided in the education system are also being studied, as there will hopefully be a substantial amount of new information available in the coming years.

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Table 1

Prevalence Rates, Assessment and Treatment Information for Psychiatric Disorders Common In 22q11.2 Deletion Syndrome

	Prevalence Rates in 22q11.2 DS†					Screening Instrument	Evidence Based Treatments	FDA approved psychopharmacological intervention for indication
	6–12 yrs	13–17 yrs	18–25 yrs	26–35 yrs	35+ yrs			
Autism	12.77%	26.54%	16.10%	---	---	Modified Checklist for Autism in Toddlers Autism Screening Questionnaire	Behavioral Therapy	For irritability associated with autism: risperidone, aripiprazole
ADHD	37.10%	23.86%	15.59%	---	---	Conner's Rating Scales, 3rd edition Vanderbilt ADHD Scales	• Behavioral parent training • Behavioral classroom management • Behavioral peer interventions • Combined behavior management interventions • Organization training • Combined training interventions	methylphenidate amphetamine dextroamphetamine atomoxetine guanfacine clonidine hydrochloride
Anxiety	35.63%	33.92%	24.07%	24.83%	27.56%	Multidimensional Anxiety Scale for Children - 2nd Edition Screen for Child Anxiety Related Emotional Disorders	• Individual Cognitive Behavioral Therapy • CBT for anxiety • Group CBT for anxiety (without parents) • Group CBT for anxiety with parents • Social skills training • Exposure treatment • Family Focused Individual CBT	For OCD only: fluoxetine, sertraline, fluvoxamine
Mood disorders	3.29%	11.85%	18.27%	14.67%	20.47%	Child Mania Rating Scale; screening questions with checklists developed from DSM symptoms	• CBT for Depression group, child only • CBT for Depression child group, plus parent component	escitalopram, fluoxetine lithium (mania)

	Prevalence Rates in 22q11.2 DS†					Screening Instrument	Evidence Based Treatments	FDA approved psychopharmacological intervention for indication
	6–12 yrs	13–17 yrs	18–25 yrs	26–35 yrs	35+ yrs			
							• Behavior therapy Family Psychoeducation plus Skill Building	
Schizophrenia spectrum disorder	1.97%	10.12%	23.53%	41.33%	41.73%	Prodromal Questionnaire-16; screening questions administered in a developmentally sensitive manner	• Cognitive behavioral therapy for psychosis (CBTp) • Social skills training • Family interventions • Supported employment • Cognitive rehabilitation	risperidone, olanzapine aripiprazole, haloperidol (psychotic symptoms)

†Prevalence rates are from the international consortium on brain and behavior in 22q11.2 DS[43] Note that these prevalence rates were based on samples ascertained from various types (psychiatric, genetic, craniofacial) of clinics and therefore may be reflective of differences in ascertainment between disciplinary clinics.