# Autism, Psychosis, or Both? Unraveling Complex Patient Presentations

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**KEYWORDS**

• Autism spectrum disorders • Schizophrenia spectrum disorders • Psychosis
• 22q11.2 deletion syndrome

**KEY POINTS**

- Autism spectrum disorders (ASDs) and schizophrenia spectrum disorders (SSDs) co-occur at elevated rates, likely in part due to shared genetic risk factors.
- Although many core features of ASD may seem similar to symptoms of psychosis, a thorough diagnostic assessment is key to differentiating features of each disorder.
- Individuals with both ASDs and SSDs may experience more severe symptoms and may be more likely to experience lack of response from multiple antipsychotic medications.
- Catatonia is a frequently overlooked psychomotor syndrome that may occur with both ASDs and SSDs. Affected individuals may require electroconvulsive therapy if they do not improve with benzodiazepines.

## INTRODUCTION

Autism spectrum disorders (ASDs) are characterized by deficits in social communication and social interaction, restricted interests, repetitive behaviors, and sensory hypo- or hyperresponsivity. These features vary substantially in severity and functional impact across individuals and must be present from early childhood. Schizophrenia spectrum disorders (SSDs), which often manifest in adolescence or young adulthood, also range in severity and include positive symptoms (eg, delusions and

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hallucinations), negative symptoms (eg, flattened affect, withdrawal), and disorganized speech or behavior. As diagnostically distinct conditions, ASDs and SSDs share multiple clinical features and genetic risk factors and seem to co-occur at elevated rates. Shared clinical features include social-emotional challenges (eg, alexithymia, theory of mind deficits), executive functioning deficits, and catatonia. Further, symptoms of one disorder may mimic the other, as illustrated by phenotypic similarities between negative psychotic symptoms (eg, social withdrawal) and reduced social-emotional reciprocity in ASD. Although presentations of comorbid ASD and psychosis pose challenges to the modern-day clinician, such dilemmas have their roots in the historical context of both disorders.

The term "autism" is credited to Swiss psychiatrist Eugen Bleuler, who described it in the early 1900s as a preoccupation with inner life while actively avoiding the external world.[1–3] Contemporaneously, German psychiatrist Emil Kraepelin described autistic-like behavior as evidence of early onset schizophrenia, writing, "we are dealing with children who have always shown a quiet, shy, withdrawn nature, engaged in no friendships and only lived for themselves."[4] Autistic features were integrated into descriptions of schizoid personality disorder by luminaries such as Ernst Kretschmer[4] and described in association with catatonia in the 1920s by Russian pediatric neurologist G. Ewa Ssucharewa.[5] Early versions of the Diagnostic and Statistical Manual (DSM) made no distinction between ASD and childhood schizophrenia, stating that latter may be characterized by "autistic, atypical, and withdrawn behavior."[6] It was not until the 1970s that ASD and childhood schizophrenia were reconsidered and redefined as separate conditions by Rutter[7] and Kolvin,[8] leading to the characterization of pervasive developmental disorders (PDD) in DSM-III.[9] Further evolution of diagnostic criteria has led to the present iteration of ASD in DSM-5, which emphasizes deficits in social communication and restricted, repetitive behaviors and interests, although ASDs and SSDs continue to be considered closely related as evidenced by their neighboring sections in the manual.[10] This historical framework provides context for the following discussion of the overlaps and distinctions between ASDs and SSDs, which will include genetic factors, affected brain regions, epidemiologic features, clinical assessment, and treatment considerations for individuals with both comorbid conditions.

## SHARED GENETIC VULNERABILITY

Genetics play a significant role in both ASD and schizophrenia with heritability estimated at about 80% for both conditions.[11] Given the overlap of ASDs and SSDs, one could hypothesize that these conditions share common genetic risk factors. Indeed, Sullivan and colleagues[12] demonstrated in a Swedish cohort that presence of schizophrenia in parents significantly increased risk for ASD (odds ratio [OR] 2.9; 95% confidence interval [CI] 2.5–3.4). Studies have implicated single genes that share overlapping dysregulation in ASD and schizophrenia,[13] common single nucleotide polymorphisms,[14] and genomic regions or genes associated with both conditions.[15,16] Copy number variant (CNV) loci, in which sections of the genome are duplicated or deleted, have also demonstrated risk for development of ASDs and SSDs. Many of the identified CNV duplication or deletion syndromes (eg, 16p11.2,[17] 22q13.3 [SHANK3][18]), while clinically relevant, only account for about 1% of cases.

ASDs and SSDs may share a reciprocal genetic relationship, in which deletions predispose an individual to one disorder and duplications to the other. Indeed,

ASDs tend to be associated with upregulation of pathways from loss of function of negative regulators, and SSDs tend to occur due to reduced pathway activation.[19] The 22q11.2 deletion syndrome (22q11.2DS), the most common chromosomal microdeletion disorder (1 in 2000–4000 live births[20]), illustrates this reciprocal genetic relationship as well as the range of clinical manifestation in individuals at risk for both ASDs and SSDs.

### *22q11.2 Deletion Syndrome*

22q11.2DS is associated with a spectrum of neuropsychiatric conditions including intellectual disability, schizophrenia, and ASD.[21] Historically these symptoms have been known as DiGeorge or velocardiofacial syndrome, but this nomenclature is now reserved for those who present with the above symptoms but do not have a 22q11.2deletion.[21] Approximately 25% of patients are diagnosed with schizophrenia, and as many as 50% of individuals will receive a diagnosis of ASD.[21,22] Critical regions of the 22q11.2 gene are associated with ASDs,[22,23] whereas others are associated with SSDs.[19] Some studies that examine the correlation between childhood autism symptoms and later psychosis show that subgroups of patients with ASD do not develop schizophrenia in adulthood. This suggests that in some individuals ASD and SSD associated with 22q11.2DS may be considered 2 unrelated phenomena associated with a single genetic variant.[24,25] The complexities of shared genetic risk are illustrated by the varied manifestations of neuropsychiatric disorders in individuals with 22q11.2DS. Further study of shared genetic markers may shed light on the causes of both ASDs and SSDs.

## BRAIN REGIONS IMPLICATED IN AUTISM AND SCHIZOPHRENIA

Although common genetic regions provide insight into the underlying cause of both ASDs and SSDs, brain imaging studies have implicated specific regions of the brain in these disorders. Areas of the brain that demonstrate overlap in ASD and schizophrenia include the corpus callosum,[26,27] fusiform gyrus,[28,29] and amygdala.[30] The amygdala represents a characteristic example of how brain region dysfunction may manifest in each condition. In ASD populations, some studies suggest that amygdala hypoactivity is implicated in theory of mind tasks,[30,31] whereas others suggest that amygdala hyperactivation may occur during facial discrimination, eye gaze,[32] and other socially and emotionally salient situations.[33] This hyperactivation is hypothesized to contribute to anxiety and rigidity commonly seen in ASDs.[34]

Similar to ASDs, studies in individuals with SSDs have shown both hypoactivation and hyperactivation of the amygdala compared with controls, and this difference seems to occur based on the social-emotional stimuli presented.[35] However, somewhat contrary to what was seen in ASD, neutral stimuli (eg, neutral facial expressions) have been found to produce hyperactivation of the amygdala[36] while there is hypoactivity in more socially salient stimuli (eg, fearful faces) compared with neutral stimuli.[37,38]

The possibility of shared etiologic mechanisms is further suggested by a 2010 brain imaging study of 660 participants that revealed lower gray matter volumes within the limbic-striato-thalamic circuitry in both individuals with ASD and schizophrenia, compared with 801 controls.[39] Brain imaging studies will likely be an increasingly valuable research tool to increase our insight into the etiology of both disorders, and more studies are needed to characterize functional connectivity patterns and the neuroanatomical basis of symptoms in patients with comorbid ASDs and SSDs.

## EPIDEMIOLOGIC FEATURES OF COMORBID AUTISM AND PSYCHOSIS

Genetic and neurocircuitry overlap provide a neurobiological basis for recent studies that indicate elevated risk for ASD in those with SSDs and vice versa. The prevalence of psychotic features in ASD populations as well as the prevalence of autistic-like traits in individuals with a diagnosis of a psychotic disorder is reviewed later.

### *Epidemiologic Features of Psychosis in Individuals with Autism*

Recent studies suggest that individuals with ASD are at elevated risk for SSDs, with prevalence rates as high as 34.8%.[40] The likelihood that an individual with ASD will develop a psychotic illness was assessed in a large nested Swedish case-control study in which researchers determined that the odds ratio for experiencing a comorbid nonaffective psychotic disorder was 5.6 (95% CI, 3.3–8.5) for individuals with ASD without intellectual disability and 3.5 (95% CI, 2.0–6.0) for individuals with ASD and intellectual disability.[41] Danish researchers estimated a similar adjusted odds ratio for schizophrenia (OR 3.3, 95% CI, 0.8–11.8) in a population of 414 ASD cases, although their results lacked statistical significance.[42] Findings from the Avon Longitudinal Study of Parents and Children (ALSPC), a large and ongoing British cohort study, similarly indicated elevated risk of psychosis in youth with ASD as well as identified risk factors for later psychotic symptoms. A study based on 8253 individuals in the ALSPC cohort showed that children diagnosed with PDD at age 8 years seemed at heightened risk (OR 8.0; 95% CI, 2.2–30.0) for later psychotic experiences, although the study suffered from low statistical power due to a relatively small number of participants meeting criteria for this diagnosis. However, of those who did meet criteria for PDD, more than half of the children reported psychotic experiences at age 13 years.[43] Potential risk factors for later psychotic symptoms were suggested by other studies of the ASPLC cohort, including an association between greater risk for psychosis and poorer early pragmatic language[44] and maternal concern regarding speech development and excessive rituals or habits.[45] In summary, these studies imply that rates of comorbidity of psychosis in ASD populations are elevated, and communication or language delays are associated with later psychotic symptoms.

### *Epidemiologic Features of Autism in Individuals with Schizophrenia*

Schizophrenia, which may be considered a developmental disorder in its own right, has been associated with a history of developmental delay since the 1990s.[46–48] Longitudinal studies of children with childhood schizophrenia (onset before age 13 years)[49] suggest high rates of comorbid ASD or other developmental delay. A 2004 National Institutes of Mental Health longitudinal cohort study indicated that of a sample of 75 children with childhood schizophrenia, 25% (n = 19) had a lifetime diagnosis of an ASD, although the majority (n = 16) met criteria for PDD rather than autistic disorder or Asperger disorder using DSM-IV-TR criteria.[50] Similarly, Rapoport and colleagues[16] characterized 97 children with childhood schizophrenia and found that a comparable proportion (28%) met criteria for a lifetime diagnosis of ASD.

Studies of adolescents and young adults with SSDs have yielded lower rates of ASD, although this is an area that requires further study. Researchers from Sweden obtained rates of comorbid diagnoses of neurodevelopmental disorders in a large cohort (n = 2091) of individuals hospitalized for first-episode psychosis between ages 16 and 25 years. They found that 5% of the individuals had a diagnosis of autism and that delusional disorder was more commonly found in the autism group (OR = 2.3, $P<.05$). The ASD group was more likely than the rest of the cohort to be taking

antipsychotic medication 2 years later, potentially suggesting that the ASD group experienced a more severe or chronic psychotic illness.[51] Taken together, these studies indicate that individuals with early onset SSDs are more likely to have a history of developmental delay or features of ASD, whereas rates of meeting full ASD criteria are mixed.

## CLINICAL PRESENTATION AND ASSESSMENT OF PSYCHOSIS IN INDIVIDUALS WITH AUTISM

Clinicians often struggle with diagnostic assessment in individuals with possible comorbid ASDs and SSDs, particularly in cases that are complex. Clinicians may be faced with the dilemma of unraveling symptoms of both conditions or ruling one condition out in favor of another one. The components of a thorough diagnostic assessment as well as potential ASD features that may be mistaken for psychosis are discussed later. Catatonia, a frequently underdiagnosed syndrome that occurs in both ASDs and SSDs is a complex condition that warrants special consideration.

### *Red Flags for Psychosis in Autism: Diagnostic Assessment*

A clinician should consider a comorbid diagnosis of a psychotic disorder in an individual with ASD who reports perceptual abnormalities or beliefs and exhibits behaviors that seem different from baseline. These symptoms, as well as a change in social, cognitive, or adaptive functioning from baseline should lead to further inquiry. Collateral information from parents, caregivers, or teachers is often crucial to sorting out what features may or may not be due to psychosis. Parents and caregivers can often identify changes in behavior from baseline, even if they are unsure of how to understand what they are observing. The value of collateral information becomes apparent, for example, during an assessment for thought disorder in a child with ASD whose verbalizations are primarily repetitive or scripted. Although scripted speech may itself seem idiosyncratic or nonsensical, often when provided with context and interpretation by others, clinicians realize that such verbalizations are a feature of ASD rather than disorganized thinking. However, if a parent or a caregiver is unable to decipher the underlying meaning of a child's thoughts and verbalizations, then concern for psychosis should increase. Similarly, monitoring for psychosis should occur, with evidence of a change in baseline social interactions, increased withdrawal, or presence of odd or unusual behaviors that do not fit with an individual's typical interests or rituals.

In addition to collateral information, a careful developmental, behavioral, medical, and psychiatric history is necessary for diagnostic clarity, as there are currently no biomarkers available to distinguish between ASDs and SSDs. A longitudinal assessment of symptoms and mental status is often helpful in clarifying the diagnosis. Appropriate diagnostic and laboratory testing to rule out a medical condition as the cause for psychosis should be obtained.[52] Genetic testing should be completed in individuals in which both conditions are suspected, starting with a microarray and then proceeding to a whole genome sequence and later whole exome sequence if indicated. A family history of psychotic symptoms may provide information regarding heritable genetic risk factors.[53]

### *Autism Spectrum Disorder Traits that Resemble Psychosis*

Core features of ASD may be mistaken for psychosis if the clinician lacks relevant clinical history or information regarding baseline functioning. The following examples illustrate potential mischaracterizations of ASD features:

- A teenager with ASD and a history of being bullied voices distrust and negative beliefs about a group of people who he feels resembles his bullies. Rigid perseverative thoughts, limited perspective taking, and difficulty reading emotions may lead to concerns that the individual is paranoid or delusional, rather than struggling with core social skills. History from family members about his social relatedness and past experience with peers, as well as reality testing and attempts to understand his fearful thoughts, may reveal that these challenges are consistent with his baseline rather than psychotic symptoms.
- A child who is highly focused on sensory input (eg, sounds) and experiences auditory hypersensitivity may seem to be preoccupied with internal stimuli when she suddenly pauses, seems to stare in the distance, and seems more disconnected and inattentive than usual. Observation when this occurs, history from others who also hear the sensory input, and careful assessment to rule out other medical causes of potential staring spells may clarify that this behavior is a feature of ASD.

The prodromal or attenuated psychosis period may present several features that overlap with ASD (eg, social withdrawal, reduced emotional expression, executive functioning difficulties),[54] leading to questions and potentially false-positive diagnoses of autism before the onset of hallucinations or delusions.[55] This underscores the need for a careful history that establishes the individual's baseline functioning while evaluating for a psychotic illness.

Table 1 illustrates the potential overlap that may occur between ASD features and psychotic symptoms, in terms of social-emotional and communication domains, thought content, and behaviors.

### *Catatonia*

Catatonia, an underrecognized psychomotor syndrome characterized by several signs and symptoms, occurs with multiple neuropsychiatric and medical causes, including ASDs and SSDs. Diagnosis is based on the assessment of fluctuations in activity level (eg, excitement, unresponsiveness, staring, withdrawal) as well as behavior and motor changes (eg, catalepsy, echopraxia, negativism, posturing, echolalia).[10] Catatonia is a DSM-5 specifier for both autism and schizophrenia, potentially creating

**Table 1**
**Overlap between core autism features and psychosis**

| | Autism | Psychosis |
|---|---|---|
| Social-Emotional Challenges | • Lack of social-emotional reciprocity<br>• Misreading social queues<br>• Restricted or flattened affect | • Social withdrawal<br>• Blunted affect<br>• Paranoia<br>• Low mood<br>• Alexithymia |
| Communication Challenges | • Language delay<br>• Echolalia | • Poverty of speech<br>• Unusual or bizarre speech |
| Unusual Thought Content | • Restricted interests<br>• Perseveration<br>• Concrete thinking<br>• Problems with perceptual processing | • Perseveration<br>• Delusions<br>• Disorganization<br>• Hallucinations |
| Behavioral Features | • Repetitive movements | • Posturing and stereotypies during catatonia |

confusion to the diagnostician when a child or adolescent with ASD develops catatonic features. Indeed, many catatonia symptoms overlap with ASD features, including mutism, stereotypic speech, repetitive speech, and seemingly purposeless activity,[56] further contributing to risk of underdiagnoses. Prevalence estimates in children vary greatly (0.6%–17%), and catatonia is also likely underrecognized and undertreated in the general child and adolescent population.[57] Two systematic studies estimate the prevalence of catatonia in ASD to be 12% to 17%.[58,59] Of note, all patients in these studies were diagnosed with comorbid catatonia after adolescence. Shorter and Wachtel have suggested that the triad of autism, psychosis, and catatonia (a so-called Iron Triangle) may encompass 3 different manifestations of the same underlying brain disorder rather than separate conditions,[4] underscoring the complex genetic relationship, pathophysiology, and treatment. The authors are not aware of large systematic treatment studies for catatonia in individuals with the comorbid psychosis and autism, although Fink and colleagues[60] proposed a medication treatment algorithm in 2006 that suggested initial use of high-dose lorazepam (6–24 mg/d) followed by electroconvulsive therapy (ECT) if there is lack of response. The literature also contains case reports that suggest the utility of a more rapid initiation of ECT over benzodiazepines.[61,62]

## TREATMENT OF PSYCHOSIS IN AUTISM SPECTRUM DISORDER POPULATIONS

The authors are not aware of large treatment studies that address medication efficacy or safety in populations of patients with comorbid autism and schizophrenia. Individuals with comorbid ASD and SSDs may be less likely to experience benefit from antipsychotics, as suggested by a 2017 study in which comorbid ASDs were significantly associated with failure of multiple (>2) antipsychotics.[63] The authors' clinical experiences suggest that earlier use of clozapine may be helpful to reduce psychotic symptoms and improve functional outcomes. There is one case report and recent small Turkish retrospective review that indicated that patients with ASD and schizophrenia experienced a reduction in psychotic symptoms with clozapine treatment.[64] Further, the authors recommend a family centered approach that includes psychoeducation, supportive therapy, and focus on functional outcomes and symptom reduction, as well as carefully monitored psychopharmacologic interventions when treating patients with comorbid ASDs and SSDs.

## FUTURE DIRECTIONS

Although there is increasing recognition of the co-occurrence of ASDs and SSDs, there have been few systematic studies of outcomes for individuals with both conditions. There is a critical need for better characterization of strategies to ensure safety, given the increased overall risk of suicidal behavior in individuals with ASDs[65] as well as a growing evidence base to suggest higher rates of depression and suicidal thinking in those with autism spectrum traits experiencing first episode psychosis.[66] In addition, better characterization of the range of clinical presentations and better recognition of catatonia will likely lead to reduced morbidity in this population.

Studies that explore the cause and genetic risk factors for individuals with comorbid ASD and SSD may lead to novel treatment approaches and improved functional outcomes given the elevated rates of co-occurrence of these conditions.

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