

Bipolar Disorder and Psychosis in Autism



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KEYWORDS

• Bipolar disorder • Psychosis • Autism • Asperger syndrome

KEY POINTS

- Bipolar disorder and psychosis are severe comorbid psychiatric disorders that can occur in persons with autism spectrum disorders (ASDs).
- Although classified as distinct conditions, they can occur together or at different times across the life span of a person with autism.
- Persons with ASD are probably at an increased risk of developing these conditions compared with the general population.
- Their diagnosis, treatments, and outcomes are complicated by the heterogeneity of ASD and by the co-occurrence of other medical and psychiatric disorders.

BIPOLAR DISORDER

In its classic form, bipolar disorder is one of the most severe psychiatric disorders that can co-occur in persons with autism spectrum disorders (ASDs). Along with depression and anxiety, it is probably the most common psychiatric disorder that occurs with autism. Before examining its comorbidity with autism, it is important to briefly review its current classification. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision (DSM-5) classifies it as bipolar I, bipolar II, and cyclothymic disorders.¹ Bipolar I disorder represents classic manic-depressive disorder when a person has a manic episode, with or without depression or psychosis. Bipolar II disorder is diagnosed in the presence of at least 1 major depressive episode and at least 1 hypomanic episode by history. Patients return to their usual levels of functioning between the episodes. People with bipolar II often first seek treatment because of depressive symptoms, which can be severe. Cyclothymic disorder represents a milder form of bipolar disorder with a history of mood swings of at least 2 years' duration. The DSM-5 also has a residual category of other specified bipolar and related disorders

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when the criteria for any of the 3 specific categories are not met. Bipolar disorder itself can be comorbid with and mistaken for several conditions, such as anxiety disorders, substance abuse, attention-deficit/hyperactivity disorder (ADHD), and oppositional defiant disorder not only in the general population but also in persons with ASDs.²

Prevalence

The exact prevalence of bipolar disorder in children with autism in the community is not clear. Some clinic-based studies have suggested high rates. For example, Worzniak and colleagues³ found that 21% of an outpatient sample of children with ASD had bipolar disorder. Somewhat higher rates have been reported in some clinical studies of adults with ASD.⁴ For example, in a study of 44 adult outpatients with ASD, Munesue and colleagues⁵ reported that 16 (34%) had a mood disorder. Out of these, 4 were diagnosed with major depression, 2 with bipolar I, 6 with bipolar II, and 4 with bipolar disorder not otherwise specified. Thus, in all, 12 (75%) were diagnosed with some form of bipolar disorder.

Presentation

Both autism and bipolar disorder may present to medical attention with the symptoms of irritability and aggression. However, these are not the core symptoms of either disorder. Although reciprocal social and communicative deficits with restricted interests and behaviors form the core features of autism, mood symptoms, particularly grandiosity, are typical of bipolar disorder. When a person with autism presents with mood and behavior changes during episodes that represent a change from the patient's usual behavior, bipolar disorder should be ruled out. However, its presentation in autism may present unique challenges⁶ depending on several factors, such as age, the subtype of bipolar disorder, the subtype of ASD, the presence of intellectual disability, and the presence of concurrent psychiatric and medical comorbidity. Sappmaz and colleagues⁷ (2018) compared 40 children with ASD with bipolar disorder with a matched group of 40 children with ASD without bipolar disorder on several rating scales (Aberrant Behavior Checklist and the Young Mania Rating Scale–Parent Version). The former group showed a “highly episodic course, with manic episodes, subsyndromal symptoms and inter-episodic periods commonly being described in the manic symptom profile of these children.”⁷ This study included children with intellectual disability; however, the ASD plus bipolar group had more patients with ADHD than the ASD-only group. Joshi and colleagues⁸ (2013) suggested that grandiosity was a dominant symptom in ASD symptoms with bipolar disorder. However, their study excluded patients with intellectual disability. In summary, classic bipolar disorder is most easily recognized in high-functioning verbal individuals with ASD by the presence of distinct alternating cycles of elated and depressed mood. The diagnostic confidence decreases with the intelligence quotient (IQ). In the low-functioning group, aggressive behavior, irritability, and hyperactivity may be more common during the hypomanic phases, whereas loss of weight and appetite, sleep disturbance, and decreased communication may be more common during the depressed phase. In addition, the symptoms may be modified by the presence of other medical and psychiatric comorbidities.

Cause

It is likely that the same factors that contribute to the cause of bipolar disorder in the general population also play a role in its comorbidity with autism. Studies have suggested that the risk of depression, including possibly bipolar disorder, is increased

in the parents of autistic children. Genetic studies have identified common genes for autism, schizophrenia, and bipolar disorder, among others.^{9,10}

Complications

Increased morbidity

Having both autism and bipolar disorder increases the functional impairment of the patient and the burden of care of the family.¹¹

Suicidal risk

Suicidal risk can be divided into suicidal ideation, suicidal behavior, and completed suicide. In clinical practice, children and adolescents with ASD are sometimes referred for threatening to kill themselves following an argument with parents when their demands are not met. In adolescents and young adults, self-injurious behaviors such as self-cutting may be accompanied by suicidal ideation. The determination of intent to die is critical in the assessment of suicide, particularly in persons with ASD, and especially in those who are lower functioning with poor verbal skills. Despite the increase of interest in suicidal behavior in persons with ASD, few systematic studies have examined this issue in persons with intellectual disability and ASD.

Psychosis

Psychotic behavior may be defined as a disorder of thought, perception, or both. Bipolar disorder, especially in its classic form, may lead to psychotic behavior both in its depressed and in its elated phase.¹²

Catatonia

Some autistic patients who initially present with bipolar disorder gradually develop symptoms of catatonia, a life-threatening condition whose diagnosis and recognition have increased in persons with ASD over the last decade. Such patients almost always have other comorbid disorders either preceding or accompanying the symptoms of bipolar disorder, underscoring the problems inherent in studying comorbidity in this population, as discussed later.

Assessment

Diagnosis of bipolar disorder in persons with ASD depends on the developmental history, age, and the level of functioning of the person. The medical work-up should include thyroid function tests to rule out hyperthyroidism. Family psychiatric history of bipolar disorder also increases the risk. The differential diagnosis includes ADHD, oppositional defiant disorder, and aggressive behavior/temper tantrums in children. Rating scales and structured interviews such as the Young Mania Rating Scale^{13,14} can also be used in persons with ASD, although they have not been validated specifically in this population.

Treatment

The goal of treatment of bipolar disorder in autism is 2-fold: to stabilize the mood and behavior and to prevent recurrence. Stabilization of severe hypomania, mania, or of depression is best done by medications with the help of psychotherapy aimed at the cognitive and adaptive level of the affected person. Several recent reports have described the use of mood stabilizers such as anticonvulsant agents and second-generation antipsychotic medications in this population.¹⁵ However, it is worth noting that patients who have autism and bipolar disorder may also have concomitant disorders such as epilepsy, ADHD, severe anxiety disorder, and psychosis, all of which should also be addressed. In the most severe and refractory cases, electroconvulsive

therapy (ECT) needs to be considered as an option.¹⁶ Depending on the age and the level of functioning, adjustments should be made in the school or vocational training program.

Course and Prognosis

As with the presence of any other comorbid psychiatric disorder, the presence of bipolar disorder complicates the course of autism and vice versa. It is difficult to perform systematic studies controlling for the other comorbid disorders, such as ADHD, which are usually present either with or preceding the onset of bipolar disorder in the setting of autism. In addition, level of IQ and communication skills also need to be taken into account. In a follow-up study of patients with bipolar disorder referred to a psychiatric clinic, 30 patients with Asperger syndrome and pervasive developmental disorder, not otherwise specified (PDDNOS), diagnosed according to DSM-IV, were identified. Subjects were more socially impaired than those who had bipolar disorder without Asperger syndrome and PDDNOS. However, patients with autistic disorder were excluded from the study.¹⁷

PSYCHOTIC DISORDERS

Defining Psychosis

Psychosis is not an easy concept to define. Although it is the core symptom of schizophrenia, it can occur in major depression, bipolar disorder, catatonia, and other conditions such as epilepsy, dementia, delirium, substance abuse, and trauma. It typically refers to a disorder of thought and/or of perception, often accompanied by a lack of insight. According to the DSM-5, which takes a narrow approach to its definition, psychosis is characterized by the presence of hallucinations without insight into their pathologic nature, delusions, or both hallucinations without insight and delusions.¹⁸ Although thought disorder per se is not required for the diagnosis of psychosis, it can be considered a diagnostic feature in the presence of extremely disorganized behavior or severe negative symptoms.

Schizophrenia

Background

Before reviewing recent publications on the comorbidity of autism and schizophrenia, it is important to reconsider the origin of their relationship. Kanner¹⁹ used the word autism to describe 11 children who formed the basis of his historic article. This term was derived from the work of Bleuler, who thought that autism was one of the 4 characteristic symptoms of schizophrenia, the others being ambivalence, alogia, and anhedonia.²⁰ Kanner¹⁹ chose the word autism to describe the isolation and withdrawal that occurs in classic autism, and not to suggest that the 2 disorders were related. Also, the disorders were described at a time when psychoanalysis was ascendant, particularly in the practice of child psychiatry in the United States. Any severely impaired child who seemed different was called psychotic, and anyone who was psychotic was schizophrenic. Because autism, as defined in the early 1940s, was a severely handicapping condition that affected the child's development in multiple ways, it was initially labeled as infantile psychosis and later as childhood psychosis/schizophrenia. In DSM-II (1968), schizophrenia, childhood type, was classified under schizophrenia as a condition "manifested by autistic, atypical, and withdrawn behavior; failure to develop identity separate from the mother's; and general unevenness, gross immaturity and inadequacy in development."²¹(p35) It was primarily the work of Kolvin and colleagues²² in the early 1970s in the United Kingdom that was instrumental in clarifying the differences between autism and schizophrenia,

comprehensively summarized by Michael Rutter²³ (1972). The DSM-III²⁴ deleted the adjective autistic in its diagnostic criteria of schizophrenia and introduced autism as the main diagnosis under pervasive developmental disorders, thus marking the separation between autism and schizophrenia. However, 40 years after the publication of DSM-III, the relationship between autism and schizophrenia continues to be controversial.

Comorbidity

One reason for the controversy is the challenge of estimating the rate of schizophrenia in persons with autism. Based on studies of narrowly defined autism, and including both high-functioning and low-functioning individuals, it is generally thought that the rate of schizophrenia in autism is the same as that in the general population. Thus, in a series of 163 patients with autism referred to a special clinic, Volkmar and Cohen²⁵ (1991) found only 1 patient with intellectual disability to meet the criteria for schizophrenia. Recent studies have reported much higher rates. For example, based on the Danish registry, Mouridsen and colleagues²⁶ reported that, in a clinic sample of 89 individuals with atypical autism, first seen as children and followed up as adults, 34.8% had at some point been diagnosed with a 'schizophrenia spectrum disorder, although atypical autism, as diagnosed by the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), autistic disorder, and Asperger syndrome were all included. Using the same dataset, they reported that the rate of schizophrenia in 118 subjects with infantile autism alone was 3.4%,²⁷ underscoring that the narrower the diagnostic criteria of autism, the lower the rate of the comorbidity between autism and schizophrenia. In a cross-sectional clinical sample of 63 high-functioning adults with ASD (DSM-IV; mean IQ, 104; mean age, 29 years), Joshi and colleagues⁸ reported that the rates of lifetime and current psychosis were 8% and 5% respectively. However, psychosis is not synonymous with schizophrenia. For example, in a long-term follow-up study of 120 individuals with autism, Billstedt and colleagues²⁸ reported that "Eight individuals (5 males, 3 females) had been diagnosed by independent (adult) psychiatrists as suffering from psychosis. Only in one individual (male) had the psychotic condition been labelled schizophrenia." Another male patient with psychosis had a diagnosis of bipolar disorder, and "there were histories suggestive of this diagnosis in four further of those receiving a diagnosis of psychosis."^{28(p356)} Thus, most of the patients in the psychosis group had a history suggestive of bipolar disorder and only 1 had been diagnosed with schizophrenia.

Similarities, Differences, and Overlap

Narrowly defined, autism is a childhood-onset disorder characterized by reciprocal social communicative deficits and restricted interests and behaviors; usually lifelong in some form; often associated with intellectual disability, other psychiatric disorders, epilepsy, and named genetic syndromes; associated with a family history of autism and related disorders; modestly responsive to behavioral and psychopharmacologic interventions; and generally marked by a less-than-optimum outcome. In contrast, schizophrenia, narrowly defined, is a late-adolescent/early adulthood-onset disorder defined by the presence of deficits of perception and thought, with no specific relationship with intellectual disability or epilepsy, although it may be overrepresented in some genetic syndromes, associated with a family history of schizophrenia and related disorders, partly responsive to pharmacologic agents, and marked by a varied outcome.²³

Although the developmental history is critical in separating the 2 conditions, some studies have suggested that autisticlike symptoms may occur in the premorbid

histories of adults with schizophrenia.²⁹ Although necessarily retrospective, these studies have highlighted the overlap that may occur between the 2 disorders, suggesting that they may start looking similar then follow separate trajectories or merge later resulting in a comorbidity. Some subtypes of individuals with ASDs may have first-degree relatives with schizophrenia-related disorders. A family genetic study of subjects with narrowly defined Asperger syndrome found that, of the 58 subjects, 9 (15%) had a family history of schizophrenia.³⁰

Molecular genetic studies have revealed shared copy number variants, deletions, and duplications such as 22q11.2, 1q21.1, and 15q13.3, and overlapping genes such as BDNF, CHRNA7, DISC1, DRD2, suggesting that the 2 disorders may be related.³¹ In addition, overlapping genes FOXP2, HTR2A, MAOA, MTHFR, SLC6A3, and TPH2 have been found to be involved both in schizophrenia and ASD. However, similar findings have been reported in other conditions, such as bipolar disorder, ADHD, and obsessive-compulsive disorder, and are not specific to the relationship between autism and schizophrenia.¹⁰

Although both patients with autism and with schizophrenia may have deficits of social cognition, subtle differences may exist between the 2 groups. Tobe and colleagues³² (2016) administered a social cognition battery using both auditory and visual emotion recognition measures to a group of 19 high-functioning individuals with ASD, 92 individuals with schizophrenia, and 73 healthy control adults. Patients with schizophrenia were impaired on both auditory and visual measures, whereas patients with ASD had intact auditory function but were impaired on visual emotion measure only.

Mentalizing deficits, which index the impairment of the ability to infer the mental states of others, have been reported in both disorders. Based on a meta-analysis of 37 studies, Chung and colleagues³³ investigated whether differences in clinical features of the 2 disorders predicted different patterns of performance on mentalizing tests. They concluded that adults with schizophrenia showed a trend toward greater impairments on verbal than on visual mentalizing tasks, whereas adults with ASD did not show different levels of impairment on the verbal versus visual tasks. In an imaging study, Toal and colleagues³⁴ (2009) compared 14 adults with ASD with psychosis, 16 without psychosis, and 16 healthy controls. The ASD groups had increased gray matter in the striatal region but less in both the temporal lobes and the cerebellum, but those with comorbid psychosis also had reduced gray matter in the frontal and occipital regions, right insular cortex, and bilaterally in the cerebellum, and reduced white matter in the cerebellum and the left lingual gyrus. Because these abnormalities differed from those reported in psychosis in general and resembled those tentatively reported in at-risk studies of psychosis in young persons, the investigators suggested that the results might represent an alternative entry point into a final common pathway of psychosis.

Assessment

Diagnosing schizophrenia in autism depends on the age of the patient, the subtype of the disorder, the presence of intellectual disability, the level of verbal skills, and the presence of other comorbid disorders. Because there is no biological test for the diagnosis of either autism or schizophrenia, the diagnosis remains clinical; rating scales and structured interviews only provide supplementary information. If an autistic child has severe intellectual disability with impaired speech, it is virtually impossible to make a confident diagnosis of schizophrenia. Between the ages of 5 and 12 years, children with autism with good verbal skills sometimes report seeing and hearing things that do not exist. However, these reports must be carefully distinguished from illusions,

overvalued ideas, misinterpretations, imaginary ideas, autistic fixations and perseverations, delayed echolalia, and so forth. If an adolescent aged between 13 and 18 years complains of symptoms suggestive of auditory and visual hallucinations, the differential diagnosis should then include depression and substance abuse disorders, which are much more common than schizophrenia in the general population. If an adult with autism and severe intellectual disability is suspected of psychosis, then the assessment should be based on techniques used in persons with intellectual disability. However, in high-functioning individuals with autism, the assessment should be based on tools used in the general population. In contrast, ruling out autism in an adult with an established diagnosis of schizophrenia or psychosis presents its own challenges. The diagnosis depends on eliciting a credible developmental history, which is not always possible. The distinction is particularly difficult in patients who have negative symptoms of schizophrenia because of the resemblance with the aloof and passive social subtypes of ASDs.

Treatment

The main objective is to stabilize the patient and ensure the safety of others. There are no specific medications that target the core symptoms of autism in general or in the presence of psychosis. Treatment of autism and psychotic behavior is essentially symptomatic. If the psychosis is secondary to another disorder, such as a severe mood disorder or substance abuse, or catatonia, that disorder should also be treated. Antipsychotic medications such as Risperdal are commonly used in patients with and without autism. Other drugs used in the treatment of schizophrenia have also been used in autism in open studies, such as Clozaril, oxytocin, and bumetanide.^{35,36} In refractory cases, ECT may be considered.³⁷ In addition, supportive and cognitive behavior psychotherapy, along with providing support to the family, should be provided depending on the clinical status of the patient. Although outcome studies of autism have not systematically studied the role of psychosis, there is clinical evidence that comorbidity in general negatively affects the long-term prognosis.

DISCLOSURE

The authors have nothing to disclose.

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