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Challenges in the diagnosis and treatment of depression in autism spectrum disorders across the lifespan

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Diagnosis and treatment of comorbid neuropsychiatric illness is often a secondary focus of treatment in individuals with autism spectrum disorder (ASD), given that substantial impairment may be caused by core symptoms of ASD itself. However, psychiatric comorbidities, including depressive disorders, are common and frequently result in additional functional impairment, treatment costs, and burden on caregivers. Clinicians may struggle to appropriately diagnose depression in ASD due to communication deficits, atypical presentation of depression in ASD, and lack of standardized diagnostic tools. Specific risk and resilience factors for depression in ASD across the lifespan, including level of functioning, age, family history, and coping style, have been suggested, but require further study. Treatment with medications or psychotherapy may be beneficial, though more research is required to establish guidelines for management of symptoms. This review will describe typical presentations of depression in individuals with ASD, review current information on the prevalence, assessment, and treatment of comorbid depression in individuals with ASD, and identify important research gaps.

Introduction

Autism spectrum disorder (ASD) is characterized both by impairments in social communication and relationships and by the presence of impairing restricted and repetitive patterns of behavior, interests, or activities.[1] Though some level of impairment must be present before 3 years of age, individuals vary greatly in terms of symptom expression and level of functioning. Up to one half of individuals are functionally nonverbal.[2] Further, a significant proportion of affected individuals have general cognitive and functional abilities consistent with intellectual disability.[3] Repetitive behaviors may interfere with learning and activities of daily living. In addition to these defining symptoms, neurocognitive issues with abstraction and generalization, alexithymia (difficulty identifying feelings) and poor understanding of others' emotions and cognitions (known as theory of mind) are common. Many affected individuals require close supervision to accomplish activities of daily living and/or

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maintain safety. Commonly associated medical problems such as epilepsy and bowel dysfunction and psychiatric problems with attention, mood, anxiety, and impulse control increase functional impairment, costs, and burden on caregivers.[4-9] Recent studies by the Centers for Disease Control and Prevention (CDC) found that 1 in 68 8-year-old children had a prior medical or educational diagnosis of ASD.[10] A population-based clinical screening study found that 2.6% of 7- to 12-year-olds in Korea were affected, two thirds of whom had not been previously diagnosed.[11] Thus, ASD represents a significant public health concern due to high prevalence, early onset, marked disability, and lifelong persistence.

The annual prevalence of depressive disorders in the general population is approximately 10%, with rates of 7.5% among adolescents. Depression itself carries an increased risk of medical illness, poor functioning in adolescence and adulthood, and death due to suicide.[12] Studies of comorbid psychiatric illness in ASD indicate high rates of depressive disorders,[13,14] though they are often under-recognized and likely undertreated. Diagnosis of Major Depressive Disorder (MDD) in the context of ASD can be particularly challenging given atypical presentations of depression in ASD, masking of common depression symptoms by features of ASD, and the lack of standardized diagnostic tools for assessment of depression in those with ASD. Little is known about the presentation, risk factors, and course of depressive illness over time as youth with ASD enter adulthood.[15] Recognition of a comorbid depressive illness has important implications for overall treatment, prognosis, and service delivery.[14] This review will describe typical presentations of depression in ASD, review available information on the prevalence, assessment, and treatment of depression in individuals with autism across the lifespan, and identify the critical gaps in our knowledge.

Presentation of depression in ASD

Two case vignettes are presented below, to highlight the key challenges in diagnosing comorbid depression in ASD. The first involves a verbal young adult. The second involves a minimally verbal school-aged child.

Case 1: Jack

Jack had been diagnosed with ASD at 30 months of age and developed phrase speech at 8 years of age. He was particularly interested in popular music and physical fitness, interacted around these interests with family and adults in the neighborhood, and was very insistent on following his routines, but had never been aggressive. Nine months before he came to the clinic, he had graduated from high school at age 22 and had begun working with a job coach at a local grocery store. His younger brother had also graduated and moved away to college. Things went well for the first few months, but then he began to have difficulty sleeping and was eating less. He began exercising for more extended periods and complained to his parents that his muscles were melting. He began to check his appearance in mirrors so frequently that it interfered with his daily activities. At the same time, he was more withdrawn and seldom talked with the neighbors any more. He was in almost constant motion, pacing, playing basketball or walking the dog. He also was more irritable and on occasion pushed furniture over when he felt others were interfering with his activities. On mental status exam, he spoke very little and often seemed preoccupied or confused. When asked about his mood he said "not good" and talked about his muscles. He said there was a black shadow coming over his arms and legs and he was not himself. His affect was irritable especially when asked direct questions. He denied any desire to hurt himself or others. He did not respond to questions about the duration of his problems, things that he enjoyed, or things that may have been upsetting. His parents were primarily concerned about his withdrawal, irritability and agitation. Family history was positive for schizophrenia, depression, and severe anxiety. His parents were reluctant to try an antipsychotic medication and he was started on fluoxetine. Within 3 months he was sleeping better, and was less physically agitated and less irritable. He no longer looked in the mirror or talked about his muscles. However, he remained more withdrawn than his baseline for 4 more months despite increases in his fluoxetine. After 1 year, his family and he felt he was back to his usual self.

Case 2: Mark

Mark had been diagnosed with ASD at age 2 and had always been in a self-contained class. His tested cognitive abilities were in the severely intellectually disabled range, and he was minimally verbal. He had almost constant self-stimulatory behaviors, but could sit in the

classroom for up to 40 minutes at a time and was able to complete about 80% of the work his teachers gave him. He would bang his head every few days when frustrated at his baseline and would sometimes become physically aggressive if people tried to restrain him. He was a very picky eater, had chronic constipation, and had always been a poor sleeper. There was a family history of depression with good response to bupropion.

When he was 9 years old, Mark's teachers, who had worked with him the previous year, expressed concern that something was wrong. He was resistant to doing more than 5 minutes of academic work, and would respond aggressively or start banging his head if pushed to do so. He seemed very easily annoyed by his classmates and was often aggressive to them for no clear reason. At home, he was also more unpredictable and was not soothed by activities or foods that he usually desired. He cried more often, would bang his head multiple times a day, and woke multiple times a night. Repeated physical exams failed to reveal any medical problems that might account for the change in his behavior. A bowel cleanout was performed, with no change in behavior. There was minimal improvement with an antipsychotic targeting his aggression and self-injury. However, the episodes of aggression and head banging were reduced by ~60% after 2 months of treatment with bupropion. His sleep returned to normal, crying was minimal, and his mother reported he seemed happier.

Clinical presentation

Common features of depression, including dysphoric mood, anhedonia, and sad affect may be difficult to recognize in people with ASD. Relatively few individuals with ASD directly express feelings of sadness, hopelessness, low self-esteem, worthlessness, excessive guilt, or suicidal ideation.[16,17] Further, individuals with ASD often have flat or constricted affect, so that changes associated with the presence of depression may be subtle. Early case reports of depression in ASD included reports of two individuals who cried for the first time in their lives, and others who appeared apathetic and unhappy.[18] Anhedonia may present as decreased interest in preferred interests, refusal to attend structured activities, or decreased response to previously motivating items or activities. The content of written or drawn communications may become increasingly morbid or morose, for example a child drawing tombstones in-

stead of a preferred subject. Some individuals may experience a regression in self-care abilities, presenting with worsening hygiene or general appearance.[18,19] In other cases there may be apparent worsening of core features of ASD, including social withdrawal and insistence on sameness, or worsening of symptoms frequently associated with ASD such as concentration deficits, agitation, aggression, or self-injury.[16,18,20] Neurovegetative symptoms such as sleep disturbance, changes in appetite or weight, and psychomotor retardation or agitation are common, and may be the most prominent signs in minimally verbal individuals. Psychotic or potentially psychotic symptoms may also herald the onset of depression. If psychotic symptoms are present, they may reflect communication difficulties, psychosis in the context of depression, or a primary psychotic illness. In all cases, the clinician should be focused on differences between the patient's baseline affect and behaviors and his/her current presentation.

Prevalence

It is widely accepted that depressive disorders occur frequently in ASD, though there is much variation in the estimated prevalence. Published 1-year prevalence rates for concurrent depression in youth with ASD range from 0.9% to 50%, with lifetime prevalence rates of depression among youth with ASD estimated to range from 10.1% to 53%.[15,21-23] In the Interactive Autism Network database, which consists of unconfirmed parent reports of symptoms and diagnoses, 11% of 4343 children had been diagnosed with depression.[23] Fairly similar results were obtained by Leyfer and colleagues who directly interviewed parents of children and adolescents between the ages of 5 and 17 years (n=109, mean age 9 years) with confirmed ASD using a version of the Kiddie Schedule for Affective Disorders and Schizophrenia that had been modified to account for possible differences in symptom presentation among youth with ASD, known as the Autism Comorbidity Interview (ACI). Specifically 10% of the participants met *DSM-IV* criteria for MDD, and an additional 14% qualified for subsyndromal depression.[2] Studies that have directly compared youth with ASD with those with typical development or similar cognitive impairments have found that those with ASD are significantly more likely to experience an episode of any psychiatric illness, most commonly MDD, and that their depressive episodes

tend to last longer.[24,25] The largest such study, conducted by Mayes and colleagues, examined parent ratings on the Pediatric Behavior Scale in 350 youth with ASD, 187 typically developing peers and 853 children with other disorders, and similarly found significantly higher rates and severity of depressive symptoms among the youth with ASD compared with either control group.[17]

The degree to which prevalence data for depression in children and adolescents can be applied to adults is unclear. The results of existing studies are inconsistent with both lower and higher rates of depression being reported in adults than in the pediatric population with ASD. A longitudinal study that followed 89 participants over ~16 years found a modest reduction in emotional and behavioral problems associated with ASD over time, including in the study's proxy measure of depression.[25] In contrast, two independent studies that solicited the involvement of all adults identified with an ASD from specific regions in Sweden and Norway respectively found higher rates of depression (37% to 70%) than reported by many other groups for younger individuals with ASD.[26,27] Consistent with studies in children with ASD, adults with ASD seem more vulnerable to depression those with other developmental disabilities or typically developing individuals.

Potential risk and resilience factors for depression in ASD

The role of specific vulnerability factors for depression in ASD requires more study, though some important patterns have emerged. Family history of depression, including in second-degree relatives, appears to increase risk for depression in ASD, while family history of ASD does not.[28] Further, comorbid depression can frequently be related to a major negative life event including significant losses, transitions in caregivers, or changes in structure or activities.[14,29]

The role of IQ in the development of depression in ASD is an area of active examination. Individuals with high-functioning ASD are often assumed to be more vulnerable to depressive disorders than their lower-functioning peers, perhaps due to relative strengths in social awareness, and greater expectations of fitting in with their peers. Many of these studies have focused on verbally fluent individuals with ASD and/or have relied on parent report of symptoms. One study that examined 95 youths 6 to 18 years old with intelligence quotients (IQs) ≥70 did not find any relationship between IQ and depression.[30] In contrast, the much larger study by Mayes et al, which included 233 high-functioning children (IQ ≥ 80), and 117 low-functioning children (IQ <80), found that the children with high-functioning ASD were significantly more depressed by parent report than low-functioning children. Additionally, high-functioning children were reported to have significantly lower self-esteem than low-functioning and typically developing children.[17] This is consistent with multiple studies in verbal adults that have found that those with higher cognitive ability, less social impairment, more self-perceived impairment, and higher rates of other psychiatric symptoms, such as anxiety and rumination, were more likely to report depressive symptoms.[19,31-33] Similarly, adults with low-functioning ASD appear less likely to be identified with depression than their high-functioning peers.[34] It is unclear to what extent high-functioning individuals with ASD are actually more vulnerable to depression than their lower-functioning peers and to what extent depression is more easily identified in verbal and more insightful individuals with ASD. It seems likely that lower-functioning individuals may be unable to self-report depressive symptoms and instead engage in increased self-injury or aggressive or destructive behavior or demonstrate increased social withdrawal or rigidity during periods of depression.[34] Such externalizing behaviors may overshadow internalizing symptoms.[19]

Many people have hypothesized that greater social desire, coupled with limited social skills and more frequent negative social interactions and/or higher frequency of bullying or rejection, may be associated with greater risk of depression among individuals with ASD. However, we are unaware of any studies specifically examining these factors with respect to incidence of depression. Similarly, it has been hypothesized that individuals with greater theory of mind difficulties, specifically difficulties appreciating the mental states of self and others and using this knowledge to understand and predict behavior, might experience more social rejection and subsequently more depressive symptoms than those with better theory of mind abilities.[35] The one study that specifically examined theory of mind score and depressive symptoms did not find any correlation; however, it is possible this finding is more reflective of difficulty recognizing and expressing one's own feelings of sadness.[36]

In contrast, reduced self-esteem and the individual's perception of one's own impairments resulting from ASD have been associated with increased risk for depression. Interestingly, there was no correlation between clinician assessments of impairment and depressive symptoms.[37] Findings are similar in studies of children with ASD; those with lower levels of self-perceived social competence endorsed higher levels of depressive symptoms.[38] Greater rumination on one's perceived impairments and lower perceived social support were also associated with increased depressive symptoms.[37] Rumination appears closely related to repetitive behaviors seen in ASD, particularly insistence on sameness, implying that individuals may essentially "get stuck" on psychological substrates in addition to interests, rituals, and routines. Similarly, rumination has been found to prospectively predict the number and duration of major depressive episodes in typically developing adults.[39]

Boys with ASD who utilized adaptive coping strategies such as seeking social support or working with others to solve a problem reported fewer symptoms of depression, while those who utilized maladaptive techniques such as acting out were more likely to report depression, supporting concerns that externalizing behaviors may be linked to underlying depression. Interestingly, youth with ASD who utilize avoidant coping styles such as cognitive restructuring, distraction, and ignoring reported lower symptoms of depression,[40] suggesting that these particular styles may be protective.

Assessment

It is essential to obtain a good description of an individual's baseline range of emotional expression and activities in order to assess sustained changes in affect and behavior over time.[18] In addition, it is important to get a good history of changes in the environment that may have precipitated a depression and of a family history of depression. Semistructured interviews designed for other populations or caregiver report measures may need to be modified or supplemented for the ASD population.[41,42] The ACI is one example of a modified screening tool.[2] During interviews it is particularly important to determine if a particular concept, such as guilt, is understood before inquiring about symptoms related the concept (eg, excessive guilt). Other concepts included in many self-report measures that are particularly vulnerable to limited

insight and communication abilities are lack of pleasure, pessimism, a sense of failure, or loss of energy.[41,42] Caregiver reports are also likely to be influenced by the scale utilized, the psychological sophistication of the reporter, and the degree to which the individual with ASD reveals his or her internalizing symptoms. Depressive symptoms may not be directly expressed, leading parents or caregivers to underestimate the extent to which depression may be impacting functioning. This was demonstrated in a study of high-functioning adolescents with ASD who reported more symptoms of anxiety or depression than their parents.[43]

Treatment

The role of psychopharmacological agents and psychosocial interventions to treat depression in ASD populations requires further study. Psychotropic medications are frequently prescribed to youth and adults with ASD, and polypharmacy is common. Of a group of 33 565 children with ASD, 64% were prescribed one psychotropic medication, 35% were prescribed two or more classes of psychotropic medication, and 15% used medications from three or more classes. Antidepressants were used in 66% of those receiving more than one class of psychotropic medication.[44] Psychotropic medication use appears to be even more common in adults with ASD than in children.[45,46] Further, antidepressant use appears increased among those with high-functioning ASD.[47,48]

Treatment for depression with antidepressant agents, typically selective serotonin reuptake inhibitors (SSRIs), is guided by evidence in typically developing individuals. Although multiple studies have failed to demonstrate the efficacy of SSRIs for improving core symptoms or repetitive behaviors in ASD, to date no studies exist to determine the efficacy of SSRIs in treating comorbid depression in youth or adults with ASD.[49,50] A Cochrane review of use of antidepressants recommended use of SSRIs for depression on a case-by-case basis.[51] However, clinical experience suggests that these agents are useful and generally safe, though individuals with ASD may be especially prone to adverse effects such as behavioral activation, irritability, akathisia, and sleep disturbance.[52] Although it is not known how frequently severe irritability symptoms in youth with ASD reflect depression, the FDA has approved two atypical antipsychotic medications (risperidone and aripiprazole) to treat irritability associated with ASD.[53]

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There is also some evidence that behavioral therapies may reduce depressive symptoms in ASD. The most widely used of these is cognitive behavioral therapy (CBT), though its efficacy in treating depressive symptoms has only been studied to a limited extent. CBT may be useful to modify maladaptive coping strategies, restructure negative thoughts, and modify cognitive inflexibility. Most CBT programs were designed for typically developing youth and subsequently adapted for the ASD population. Many programs focus on anxiety, aggression, or core deficits rather than on depression alone,[54] though these factors are likely closely linked. A small study of group CBT focused on identifying feelings, thoughts, and behaviors, expressing feelings appropriately, and using cognitive restructuring and stress reduction techniques found a significant reduction in depressive symptoms compared with the waitlist control group after nine sessions. The observed improvement was sustained at 3- and 9-month follow-up assessments.[55]

Mindfulness-based therapies may also prove to be a useful therapeutic technique to reduce depression in ASD populations. This method encourages individuals to identify feelings or thoughts in the present moment and accept them, as they appear without analysis or discussion,[56] an approach that may be well suited to those with theory of mind and communication deficits. One randomized controlled trial of adults with ASD found a significant reduction in depression, anxiety, and rumination in the intervention group compared with the control group.[57] In addition, social and vocational skills programs may reduce depressive symptoms in adolescents and adults with ASD, even though they are not focused on depressive symptoms. Investigators found that participation in an 8-week structured group intervention resulted in lower scores on the Beck Depression Inventory-II, though the effect size was small. Individuals appeared to benefit from meeting others with similar challenges and initiating connections with each other outside of the group.[58]

The role of family therapy interventions in ASD is an area of recent but active study, as family systems are often profoundly affected by the impairments associated with ASD. Researchers are beginning to understand the complex and bidirectional influences a family member with ASD has on individual family members, including siblings, and the family system as a whole. It is understood that high levels of parental psychopathol-ogy or stress appear to predict increased ASD symptom severity and emotional or behavioral symptoms in typically developing siblings.[59] Further, high levels of expressed emotion or criticism in families appear to worsen internalizing and externalizing behaviors, as well as core features of ASD.[60] We are not aware of any formal programs that utilize family therapy as a component of treatment for depression in ASD; however programs that build on existing strengths and provide psychoeducation and support to family systems may be extremely useful in not only reducing family stress and improving quality of life, but also in improving behavior problems over time in children, adolescents, or adults with ASD.

Research priorities

Although it is clear that depression is an issue for individuals with ASD, relatively little rigorous information is available to evaluate the true scope of the problem or appropriate treatment and management of depression in this large segment of the population. It will likely be useful to conduct larger population-based cross-sectional studies and longitudinal studies that use assessment measures modified for individuals with autism in order to more accurately determine the true prevalence of comorbid depression in ASD across the lifespan. Such studies would also provide more information about typical presentations of depression, particularly among those with more limited communication skills and insight into their own feelings. In addition, it is essential that we evaluate specific pharmacologic and behavioral treatments for individuals with comorbid ASD and depression. Studies of SSRIs in individuals selected on the basis of comorbid depression and ASD seem especially important. These studies should include some focus on minimally verbal individuals since they are less likely to benefit from the available psychological interventions.

Conclusions

In summary, depression appears to occur with greater frequency among people with ASD than in the general population. There are suggestions that the risk for comorbid depression increases with age. Although current studies suggest that high-functioning, verbal individuals with ASD may be at higher risk, it is unclear

to what degree this finding is an artifact of current assessment tools and limited communication abilities of lower-functioning individuals. Therefore clinicians, parents, and caregivers must recognize that depression may present with a myriad of symptoms other than dysphoric mood in persons with ASD. Depression should be considered when individuals with ASD experience a significant change in their level of functioning or an increase in maladaptive behaviors. Clinicians who are unaccustomed to diagnosing or treating ASD populations may be poorly equipped to tease apart features

of ASD from a comorbid depressive illness. In turn, individuals with marked communication and theory of mind deficits may struggle to report depressive symptoms. Nonetheless, these symptoms may carry substantial additional morbidity and even potential mortality due to suicide,[61,62] that necessitates rapid recognition and treatment. Standardized tools are needed to assist clinicians in the diagnosis of depression among those with ASD, and more research is needed to elucidate effective psychopharmacologic and psychosocial treatment strategies. ❏

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Desafíos en el diagnóstico y tratamiento de la depresión en los trastornos del espectro autista a lo largo de la vida

En los sujetos con un trastorno del espectro autista (TEA) el diagnóstico y tratamiento de la enfermedad neuropsiquiátrica comórbida es a menudo un foco secundario de la terapia, dado que el deterioro principal puede estar causado por los síntomas nucleares del TEA propiamente tal. Sin embargo, las comorbilidades psiquiátricas, incluyendo los trastornos depresivos, son comunes y frecuentemente se traducen en adicionales deterioros funcionales, costos del tratamiento y carga para los cuidadores. Los clínicos pueden tener dificultades para diagnosticar adecuadamente la depresión en el TEA debido a los déficits de comunicación, la presentación atípica de la depresión en el TEA y la falta de herramientas diagnósticas estandarizadas. Si bien se han sugerido factores de resiliencia y riesgo específico para la depresión en el TEA a lo largo de la vida como el nivel de funcionamiento, la edad, la historia familiar y el estilo de adaptación, se requiere de más estudio. El tratamiento medicamentoso o la psicoterapia pueden ser útiles, aunque se requiere de más investigación para establecer guías de manejo de los síntomas. Este artículo describe las presentaciones típicas de la depresión en sujetos con TEA, revisa la información actualizada sobre la prevalencia, evaluación y tratamiento de la depresión comórbida en estos individuos e identifica importantes vacíos de la investigación.

Les enjeux du diagnostic et du traitement de la dépression dans les troubles autistiques au long de la vie

Le diagnostic et le traitement des maladies neuropsychiatriques comorbides sont souvent un axe secondaire du traitement des individus ayant un trouble du spectre de l'autisme (TSA), une détérioration importante pouvant être causée par les symptômes de fond du TSA lui-même. Cependant, les comorbidités psychiatriques, dont les troubles dépressifs, sont courantes et entraînent fréquemment un handicap fonctionnel supplémentaire, des coûts pour les traitements et une charge pour les soignants. Il est parfois difficile pour les médecins de diagnostiquer de façon adéquate la dépression dans les TSA à cause des déficits de communication, de la présentation atypique de la dépression et du manque d'outils diagnostiques standardisés. Les risques spécifiques et les facteurs de résilience pour la dépression dans les TSA au long de la vie, y compris le niveau de fonctionnement, l'âge, les antécédents familiaux et le mode d'adaptation ont été suggérés, mais nécessitent d'être étudiés. Des traitements médicamenteux ou psychothérapiques peuvent être bénéfiques, mais il faut d'autres recherches pour établir des recommandations pour la prise en charge des symptômes. Cet article décrira les présentations typiques de la dépression chez les personnes atteintes de TSA, reconsidèrera l'information actuelle sur la prévalence, l'évaluation et le traitement de la dépression comorbide chez les personnes atteintes de TSA et identifiera les lacunes importantes de la recherche.

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