Buspirone for Comorbid Anxiety in Autism

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In 2021, the Centers for Disease Control (CDC) released an analysis of newer data collected in 2018 indicating that the prevalence of autism spectrum disorders (ASD) in 8-year-old children is 1 in 44 (2.3%), and boys are 4 times more likely to have ASD compared to girls.[1] Amid these developments, there is emerging evidence about the presence of highly comorbid disorders in individuals with ASD. About 70% of youth with ASD experience at least 1 comorbid psychiatric disorder, whereas nearly 40% of individuals may have 2 or more psychiatric disorders.[2] The narrow criterion for inpatient treatment of patients with ASD is based on risks entailed due to the severity of the comorbid disorders. In 2011, 40% of youth with ASD were estimated to have comorbid anxiety[3]; however, more recent analysis points toward a broader range of 1.5%–54% across many studies.[4] The risk factors for anxiety are multifactorial,[5] and like many disorders, it shares polygenic risks with ASD.[6]

In clinical practice, multiple issues are encountered. First, there are concerns about inadequate tools to measure anxiety in individuals with ASD since its symptoms overlap with other disorders.[7] Second, there are questions about lack of efficacy and serious behavioral activation, such as hyperactivity, agitation, and sleep disturbances, associated with the use of selective serotonin reuptake inhibitor (SSRI) antidepressants.[8] Third, the short length of inpatient stays provides a narrow window to accurately diagnose anxiety in ASD and intervene.

Case Report

A 13-year-old girl was admitted to the hospital post serious overdose on 300 mg of escitalopram. She presented with worsening symptoms of low mood, anxiety, and auditory hallucinations. She had a 1½-year history of affective illness and was refractory to outpatient provider trials of 16 weeks of fluoxetine (dose range, 10 mg–30 mg), 10 weeks of sertraline (dose range, 25 mg–100 mg), and 6 weeks of escitalopram (dose range, 5 mg–15 mg). The family reported that her symptoms worsened with an increase in SSRI dose. She also had received 6 months of supportive psychotherapy with minimal improvement. She reported that bullying in school, constant worries about her future, and hopelessness due to lack of response to treatment precipitated the overdose of prescription escitalopram. The auditory hallucinations started 2 months ago, and she reported hearing nonspecific whispers with no clear content when she was alone, mainly in the evenings with no aggravating or relieving factors.

After the clinical assessment, she was diagnosed with major depressive disorder unspecified with psychotic symptoms and generalized anxiety disorder (GAD) per *DSM-5* criteria. She also met *DSM-5* criteria for ASD based on her detailed developmental history. Her core deficits included poor eye contact, impairments in the social pragmatic use of language, difficulties in establishing friendships, and poor prospective-taking skills (ability to consider a situation from a different point of view), although she was an honor roll student. She followed rigid routines, and her interests were narrow, which included preoccupation with technology and unusual sensory responses to loud noises and tight clothes.

There was no medical comorbidity or any trauma or substance use. She was subsequently started and maintained on a lower dose of duloxetine 20 mg given the history of her symptoms worsening with an increase in SSRI dose. Duloxetine was augmented with aripiprazole 2 mg for auditory hallucinations. She had a poor response to the combination regimen after 2 weeks of treatment. Her psychotic symptoms improved, but she continued to struggle with low mood, anxiety, and ongoing suicidal thoughts. Subsequently, duloxetine was tapered off, and buspirone was started at a low dose of 2.5 mg/d and then slowly increased to 5 mg twice/d over a week.

Her symptoms were measured on the Patient Health Questionnaire Modified for Teens[9] and Screen for Child Anxiety Related Emotional Disorders (SCARED).[10] She was provided psychoeducation about the ASD diagnosis and the rationale for the change in treatment regimen. There was a significant response with buspirone, with improvement of anxiety symptoms and a reduction in SCARED scores from 55 to 18 in 2 weeks. She was discharged to the partial hospital after a 4-week inpatient stay.

Discussion

There are no approved pharmacologic treatments for the core ASD symptoms.[11] Although treatment of comorbid clinical conditions is central to the inpatient level of care, there is a dearth of psychopharmacologic options for comorbid anxiety associated with ASD.

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Box 1. Key Points

Buspirone for the treatment of comorbid anxiety in ASD

- A higher prevalence of comorbid psychiatric conditions in ASD has been seen (70% have at least 1 and 41% more than 1).[2]
- 1.5%–54% of youths with ASD have comorbid anxiety.[4]
- In neurotypical youths, buspirone is usually well tolerated, is less likely to have adverse effects, and has a low effect size.
- Two weak but specific studies (open-label[18] and a retrospective chart review[19]) have shown positive results.
- A Cochrane meta-analysis[8] found no evidence of the efficacy of SSRIs in children with ASD but did find emerging evidence of harm.

Abbreviations: ASD = autism spectrum disorder, SSRI = selective serotonin reuptake inhibitor.

Buspirone was originally developed to treat psychoses, but in 1986, Bristol-Myers Squibb promoted it as a pharmacologically unique azapirone molecule, and it was approved by the US Food and Drug Administration (FDA) for the treatment of GAD in adults.[12] Although, there were no concerns about safety, buspirone was not FDA approved for treating GAD in children and adolescents due to limited empirical evidence about its efficacy.[13] Buspirone is a partial agonist at presynaptic and postsynaptic 5-HT_{1A} receptors. Its antianxiety effects are postulated to be due to diminished firing of serotonergic neurons resulting from presynaptic 5-HT_{1A} agonism.

Buspirone is known for its rapid absorption and is extensively metabolized to 1-pyrimidinylpiperazine (1-PP).[14] There is established empirical evidence associating behavioral activation with SSRIs in individuals with ASD. A Cochrane review[8] suggested potential harm associated with SSRI use due to the possibility of behavioral activation in individuals with ASD. There are several hypotheses for the activation associated with SSRIs, including a decrease in 5-HT, since presynaptic 5-HT_{1A} receptors are inhibited by an increase in synaptic 5-HT.[15] Akathisia is relatively uncommon with SSRIs but is postulated to be due to an imbalance between dopamine and 5-HT, with a relative enhancement of serotonergic activity.[16] Buspirone is a partial 5-HT_{1A} agonist and has minimal anti–5-HT effects, which may explain the reduced possibility of activation and akathisia. In neurotypical youth, buspirone is well tolerated, is less likely to have adverse effects, and has a low effect size.[17] An open-label study[18] of buspirone showed improvement in anxiety and irritability in ASD. Another retrospective chart review of 31 patients with high-functioning ASD found significant improvement in 58% and mild improvement in 29% of patients.[19] A randomized clinical trial showed favorable findings for the adjunctive use of buspirone with risperidone to reduce irritability.[20] It was also found to be useful in treating restrictive and repetitive behaviors at low doses.[21] There are no reports of buspirone linked with behavioral activation. Despite support of these low levels of empirical evidence,[19] use of buspirone has been limited in clinical practice (Box 1).

Individuals with ASD are likely to experience more severe adverse effects than their typically developing counterparts. Although a few patients do respond to an SSRI,[22] the increased risks of side effects and worsening of suicidal thoughts are indicators to switch to alternative treatments. In youth with ASD, failed trials with SSRIs are frequent, and the off-label use of aripiprazole as an antidepressant is also widespread.[23] Likewise, α-agonists and benzodiazepines have also been used off label to treat anxiety in ASD with no empirical support.[24] Propranolol has shown positive cognitive effects in ASD but needs further investigation.[25]

A late diagnosis of ASD is not uncommon, and diagnostic challenges add to the complexity of clinical management. Therefore, there is an increased need for psychoeducation for patients and their families. Without this knowledge, it is difficult to explain the rationale for starting low and going slow with SSRIs. In many instances, discontinuing an SSRI is prudent; however, the value of informed consent and assent cannot be underestimated.

Buspirone use in individuals with ASD is supported by the low level of clinical evidence, with only 2 low-power randomized control trials over the last decade suggesting potential benefits.[20,21] This case report adds to the scarce evidence base and suggests the need for further investigation into the therapeutic potential of buspirone in individuals with ASD.

Conclusion

Buspirone is a useful alternative to mitigate highly comorbid anxiety symptoms in ASD. With a very limited repertoire of approved and off-label psychopharmacologic agents in highly complex high acuity settings, well-tolerated buspirone may be an option worth considering.

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