SPECIAL ARTICLE: Korean Practice Guideline for Autism Spectrum Disorder
J Korean Acad Child Adolesc Psychiatry 2024;35(1):39-43
https://doi.org/10.5765/jkacap.230006

eISSN 2233-9183

Common Comorbid Condition of Patients With Autism Spectrum Disorder and Pharmacotherapy for Patients With Autism Spectrum Disorder

Un Sun Chung[1] and Ji-Hoon Kim[2]

[1]Department of Psychiatry, Kyungpook National University, School of Medicine, Daegu, Korea
[2]Department of Psychiatry, Pusan National University, School of Medicine, Yangsan, Korea

This article describes common comorbid condtion of the autism spectrum disorder (ASD) and recommends treatment guidelines of pharmacotherapy for patients with ASD. More than 95% of people with ASD have at least one additional disorder and guidelines how to evaluate and treat comorbid conditions in patients with ASD and 7 recommendations for treatment with medication for ASD.

Keywords: Autism; Comorbidity; Pharmacotherapy; Guideline.

Received: January 30, 2023 / **Revised:** March 27, 2023 / **Accepted:** December 18, 2023

Address for correspondence: Ji-Hoon Kim, Department of Psychiatry, Pusan National University School of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea
Tel: +82-55-360-3591, Fax: +82-55-360-3591, E-mail: pnuhcap@gmail.com

COMORBID CONDITIONS OF AUTISM SPECTRUM DISORDER

The American Psychiatric Association recently highlighted that more than 95% of people with autism spectrum disorder (ASD) have at least one additional disorder, and that many people have multiple types of comorbid difficulties [1]. These coexisting conditions include intellectual disability, sleep, eating and elimination problems, epilepsy, gastrointestinal disorders, cerebral palsy, brain lesions, speech problems, visual and hearing disorders, genetic disorders, Tourette syndrome, and a wide range of emotional and behavioral problems, and typical coexisting disorders are anxiety disorders, mood disorders, and attention deficit hyperactivity disorder (ADHD) [2-4]. However, the symptoms overlap and certain symptoms are so pronounced that the process of diagnostic overshadowing is common. In addition, the symptoms may be different from those typical of normally developing children.

Moreover, it is complex and difficult to assess, diagnose, and treat coexisting diseases or conditions in people with ASD due to delayed language development, communication difficulties such as mutism, and delayed intellectual development [5,6]. Appropriate treatment should be given for all accompanying medical conditions, but in many cases it is difficult to obtain adequate medical care [7].

Although there are methodological limitations in clearly identifying the prevalence of comorbid disorders in ASD patients, anxiety disorders and attention problems have been increased [8]. If there are increased irritability and behavioral changes, common ear infections or eczema might be the cause [9]. In infants, it is necessary to check for abnormalities in hearing and vision. Since it is particularly difficult to make infants sleep and feed them even before ASD is diagnosed, ASD should be prioritized and screened when these parenting difficulties are prominent [9].

Although delayed intellectual development is not essential to the diagnosis of ASD, the assessment and diagnosis of cognitive function is essential to the planning and implementation of the treatment process. In most epidemiologically based samples of persons with autistic disorder, approximately 50% exhibit severe or profound intellectual disability, 35% exhibit mild to moderate intellectual disability, and the remaining 20% have intelligence quotients (IQs) in the normal range [5]. According to recent studies, more children with ASD have IQs higher than 70 than before because applying the "spectrum" to the diagnostic name included a large number of cognitively normally developing children [10]. People with ASD generally have more difficulty communicating verbally than nonverbal ones, but some people (equivalent to Diagnostic and Statistical Manual of Mental Disorders Fourth Edition [DSM-IV] Asperger's disorder) have better verbal skills [5].

ADHD, obsessive-compulsive symptoms, self-harm, aggression, stereotypy, and tics are often accompanied and defining these behavioral problems as comorbid disorders and deciding whether to add another diagnosis is a complex process [5]. Emotional symptoms are also commonly observed, with large mood swings and inappropriate emotional reactions, and anxiety or depression [5]. Difficulty in regulating emotions leads to relatively little activity or too much activity. Depressive disorders are particularly common in adolescents with Asperger's disorder. It can also be accompanied by bipolar disorder and tic disorder, as well as Tourette's disorder, in which vocal and motor tics appear together.

The likelihood of being bullied by peers or being a victim of violence increases when attending a regular school rather than a special school [5]. Concentration problems are common, which can hinder the development of cognitive, linguistic, and social skills. In DSM-5, the diagnostic criteria were changed to allow the diagnosis of ASD and ADHD to be made together, and it is noteworthy that a large normal-controlled study showed that 49% of ASD people with concentration problems responded to methylphenidate treatment [5].

In order to reduce the risk of early death and to achieve physical and mental health, the needs of each ASD patient must be recognized and tailored medical services must be provided. Because comorbid disorders compromise the life quality of ASD patients and their family, treatment plan require more creativity and perseverance above approach for a normal child. In particular, it is recommended that the main therapist and a number of specialized medical departments (pediatrics, internal medicine, family medicine, neurology, genetics, psychiatry, rehabilitation medicine, etc.) collaborate, discuss and consult one another as a team.

PHARMACOTHERAPY

There are no drugs to treat the qualitative impairment of social interaction and repetitive behavior or restrict interest effectively. However, drugs may improve comorbid conditions, lead to positive effects on development and increase the effects of special education or other treatment programs for reducing serious behavior.

General principles are as follows:

• Clinicians should define target symptoms and use effective drugs for target symptoms. Drugs are effective on symptoms related to comorbid disorders (anxiety, depression, etc.), aggression, self-injurious behavior, hyperactivity, compulsive behavior, repetitive or stereotyped behavior, and sleep problems.

• There are no drugs to definitely improve social interaction.

• Pharmacotherapy should be done evidence-based.

• Clinicians should have expert knowledge and experience with drugs and comorbid disorders.

• Pharmacotherapy should be done after giving the effects and adverse effects to persons with ASD and their caregivers.

• Pharmacotherapy should start with a low dose, increase slowly, and define the lowest effective dose.

• The effect and adverse effects of drugs are carefully monitored by the caregiver's report and direct observation periodically.

• Scales may help to assess the effects of drugs.

• The effects and adverse effects of the drug are assessed after starting drugs at 3–4 weeks. The drugs have poor effects after 6 weeks, clinicians should stop those drugs [11].

• Adverse effects may be controlled to decrease the dose of drugs or add other drugs that reduce adverse effects. Or the clinician considers changing to other drugs.

• Clinicians should define symptoms of comorbid disorders and adverse effects of drugs and should give profit prescriptions.

Dopamine antagonists

Risperidone and aripiprazole are the most frequently used drugs for ASD. Both drugs are approved by U.S. Food and Drug Administration (FDA) for treating irritability. Risperidone is approved for 5–16 years old, and aripiprazole is approved for 6–17 years old [12,13].

Both drugs are effective in physical aggression, stereotyped behavior, and hyperactivity [14-18].

Haloperidol is approved by European Medicines Agency (EMA) to control serious aggressive behavior, in case of no effective treatment or serious adverse effects to other drugs [19].

The studies of olanzapine or other dopamine antagonists are not enough. Adverse effects of dopamine antagonists are extrapyramidal symptoms like dystonia, akathisia, and parkinsonism. Some drugs may make somnolence.

Stimulants and atomoxetine

Methylphenidate improved hyperactivity in children with ASD and ADHD. However, it was less effective and had more adverse events compared with using for children with ADHD only [20,21].

Atomoxetine also improved hyperactivity in children with ASD. However, there was no improvement in global function [22]. Methylphenidate and atomoxetine can not improve core symptoms of ASD, though both drugs can improve hyperactivity. The most frequent adverse events are decreased appetite, nausea, and headache. However, these symptoms should be distinguished from symptoms of ASD or comor-

bid disorders.

Mood stabilizers

Mood stabilizers can be used for the improvement of irritability and can improve aggressive behaviors. Valproic acid with 76 mg/mL of blood concentration was not effective to decrease irritability [23], but other studies reported improving irritability with the same blood concentration [24]. Both studies reported skin rash. There were no studies on the improvement of behavioral symptoms with lithium and lamotrigine.

Antidepressants

Though selective serotonin reuptake inhibitors (SSRIs) are most frequently prescribed in anxiety, and obsessive-compulsive symptoms. There was no prominent improvement in repetitive behavior in ASD [25,26]. Therefore, SSRIs can be used to decrease anxiety or depressive symptom in persons with ASD rather than using improved repetitive behavior. Studies of tricyclic antidepressants and serotonin-norephinephrine reuptake inhibitors are insufficient.

Melatonin

Melatonin can be used for sleep problems. The controlled-release form was effective in the increase of total sleep time and decrease of sleep latency [27]. An immediate-release form is also effective in the decrease of sleep latency [28]. Melatonin should be prescribed by professionals with knowledge of sleep control and should be checked for adverse events and effects periodically.

α-agonists

Clonidine reduces irritability, hyperactivity, hyperarousal behavior, and social interaction [29,30]. Guanfacine decreases hyperactivity and impulsivity [27]. Somnolence is the most common adverse effect.

Others

Some studies reported oxytocin increases social recognition and social function [31,32]. However, oxytocin has no effects on social recognition and stereotype behavior in meta-analysis [33]. N-acetylcysteine (NAC), D-cycloserine, and memantine are not effective in the improvement of social interaction and stereotype behavior [34-37]. Therefore, further studies are needed in the future.

An Internet search yields extensive information about ASD diagnostic tests and treatments. Wrong information about treatment, which is not clearly proven through research and is not recommended, causes the ASD patients and their family to make the wrong treatment decision.

Such tests and treatments include hair analysis, celiac antibodies, allergy tests (particularly food allergies to gluten, casein, candida, and other fungi), immunological or neurochemical abnormalities, micronutrients such as vitamins, intestinal permeability tests, stool analysis, urine peptides, mitochondrial disorders (including lactate and pyruvate), or red blood cell glutathione peroxidase tests [38].

It is also important to clearly understand that there is no association between ASD and MMR (measles, mumps, and rubella) vaccines. Due to misinformation about the vaccine, many parents do not vaccinate their children with MMR vaccine, and measles, which had been eradicated, is re-emerging in many parts of the world [39].

Again, there are currently no medications to treat the core symptoms of ASD and so-called alternative therapies (neurofeedback, facilitated communication, auditory integration training, omega-3 fatty acids, secretin, chelation, hyperbaric oxygen therapy, elimination diet without eating certain food, etc.) is not effective in treating the core features of ASD. Therefore, it is recommended not to use it [40-42].

When treating patients with ASD, clinicians must ask if they are using alternative therapies, and if so, what benefits they expect from those therapies, and discuss the risks. Although there is little scientific evidence that many alternative therapies are effective for children with ASD, families often try such therapies [43].

Clinicians should be aware of parents' motivation to seek out and apply all available therapies and be able to discuss these attempts with parents [5]. Although in most cases there is little or no benefit and the risk is not very high, some treatments have direct dangerous consequences. Examples include increased disease incidence and mortality associated with chelation therapy, and side effects caused by contaminants contained in health foods known as natural remedies [44].

It may also result in indirect risks, such as financial hardship or abandonment of other appropriate treatments or resources resulting from preoccupation with these alternative therapies. The most important thing is an atmosphere in which ASD patients and their families can openly talk about alternative therapies with clinicians, so that more appropriate evidence-based treatments can be selected [45].

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Ji-Hoon Kim, Un Sun Chung. Data curation: Ji-Hoon Kim, Un Sun Chung. Formal analysis: Un Sun Chung. Fund-

ing acquisition: Un Sun Chung. Investigation: Ji-Hoon Kim, Un Sun Chung. Methodology: Ji-Hoon Kim, Un Sun Chung. Project administration: Ji-Hoon Kim. Resources: Ji-Hoon Kim, Un Sun Chung. Software: Ji-Hoon Kim, Un Sun Chung. Supervision: Ji-Hoon Kim, Un Sun Chung. Validation: Ji-Hoon Kim. Visualization: Ji-Hoon Kim, Un Sun Chung. Writing—original draft: Ji-Hoon Kim, Un Sun Chung. Writing—review & editing: Ji-Hoon Kim, Un Sun Chung.

ORCID iDs

Un Sun Chung https://orcid.org/0000-0003-3871-1425
Ji-Hoon Kim https://orcid.org/0000-0001-8132-2359

Funding Statement

This study was supported by the Ministry of Health and Welfare, Behavior and Development Center, and the Headquarter of the National Autism and Developmental Disorder Centers.

REFERENCES

1) **American Psychiatric Association.** What is autism spectrum disorder? [Internet]. Washington, DC: American Psychiatric Association [cited 2021 Aug 31]. Available from: https://www.psychiatry.org/patients-families/autism/what-is-autism-spectrum-disorder.
2) **Lai MC, Kassee C, Besney R, Bonato S, Hull L, Mandy W, et al.** Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry 2019;6:819-829.
3) **Rosen TE, Mazefsky CA, Vasa RA, Lerner MD.** Co-occurring psychiatric conditions in autism spectrum disorder. Int Rev Psychiatry 2018;30:40-61.
4) **Soke GN, Maenner MJ, Christensen D, Kurzius-Spencer M, Schieve LA.** Prevalence of co-occurring medical and behavioral conditions/symptoms among 4- and 8-year-old children with autism spectrum disorder in selected areas of the United States in 2010. J Autism Dev Disord 2018;48:2663-2676.
5) **Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M, et al.** Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2014;53:237-257.
6) **Mason D, Ingham B, Urbanowicz A, Michael C, Birtles H, Woodbury-Smith M, et al.** A systematic review of what barriers and facilitators prevent and enable physical healthcare services access for autistic adults. J Autism Dev Disord 2019;49:3387-3400.
7) **Fuentes J, Hervás A, Howlin P; ESCAP ASD Working Party.** ESCAP practice guidance for autism: a summary of evidence-based recommendations for diagnosis and treatment. Eur Child Adolesc Psychiatry 2021;30:961-984.
8) **Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, et al.** Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord 2006;36:849-861.
9) **New York State Department of Health.** Clinical practice guideline on assessment and intervention services for young children with autism spectrum disorders (ASD): 2017 update [Internet]. Albany, NY: New York State Department of Health [cited 2017 Oct 31]. Available from: https://www.health.ny.gov/publications/20152.pdf.
10) **Christensen DL, Braun KVN, Baio J, Bilder D, Charles J, Constantino JN, et al.** Prevalence and characteristics of autism spectrum disorder among children aged 8 years — autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill Summ 2018;65:1-23.
11) **National Institute for Health and Care Excellence.** Autism spectrum disorder in under 19s: support and management [Internet]. London: National Institute for Health and Care Excellence [cited 2020 Nov 20]. Available from: https://www.nice.org.uk/guidance/cg170.
12) **Jaselskis CA, Cook EH Jr, Fletcher KE, Leventhal BL.** Clonidine treatment of hyperactive and impulsive children with autistic disorder. J Clin Psychopharmacol 1992;12:322-327.
13) **Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD.** A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry 1992;53:77-82.
14) **Scahill L, McCracken JT, King BH, Rockhill C, Shah B, Politte L, et al.** Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. Am J Psychiatry 2015;172:1197-1206.
15) **U.S. Food and Drug Administration.** Highlights of prescribing information: Risperidone. Silver Spring, MD: U.S. Food and Drug Administration [cited 2020 May 5]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020272s082,020588s070,021444s056lbl.pdf.
16) **U.S. Food and Drug Administration.** Drugs@FDA: FDA-approved drugs: Aripiprazole (products on NDA 021436) [Internet]. Silver Spring, MD: U.S. Food and Drug Administration [cited 2020 May 5]. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021436.
17) **Kim HW, Park EJ, Kim JH, Boon-Yasidhi V, Tarugsa J, Reyes A, et al.** Aripiprazole for irritability in asian children and adolescents with autistic disorder: a 12-week, multinational, multicenter, prospective open-label study. J Child Adolesc Psychopharmacol 2018;28:402-408.
18) **Ichikawa H, Mikami K, Okada T, Yamashita Y, Ishizaki Y, Tomoda A, et al.** Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder in Japan: a randomized, double-blind, placebo-controlled study. Child Psychiatry Hum Dev 2017;48:796-806.
19) **Kent JM, Kushner S, Ning X, Karcher K, Ness S, Aman M, et al.** Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. J Autism Dev Disord 2013;43:1773-1783.
20) **Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al.** A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. J Am Acad Child Adolesc Psychiatry 2009;48:1110-1119.
21) **McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, et al.** Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. Am J Psychiatry 2005;162:1142-1148.
22) **European Medicines Agency.** Haloperidol [Internet]. Amsterdam: European Medicines Agency [cited 2020 May 5]. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/haldol-associated-names.
23) **Hellings JA, Weckbaugh M, Nickel EJ, Cain SE, Zarcone JR, Reese RM, et al.** A double-blind, placebo-controlled study of valproate for aggression in youth with pervasive developmental disorders. J Child Adolesc Psychopharmacol 2005;15:682-692.
24) **Hollander E, Chaplin W, Soorya L, Wasserman S, Novotny S, Rusoff J, et al.** Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. Neuropsychopharmacology 2010;35:990-998.
25) **Williams K, Brignell A, Randall M, Silove N, Hazell P.** Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2013;8:CD004677.
26) **Goel R, Hong JS, Findling RL, Ji NY.** An update on pharmacotherapy of autism spectrum disorder in children and adolescents. Int Rev Psychiatry 2018;30:78-95.
27) **Harfterkamp M, van de Loo-Neus G, Minderaa RB, van der Gaag**

RJ, Escobar R, Schacht A, et al. A randomized double-blind study of atomoxetine versus placebo for attention-deficit/hyperactivity disorder symptoms in children with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 2012;51:733-741.
28) **Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D.** Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012;21:700-709.
29) **Research Units on Pediatric Psychopharmacology Autism Network.** Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. Arch Gen Psychiatry 2005;62:1266-1274.
30) **Sturman N, Deckx L, van Driel ML.** Methylphenidate for children and adolescents with autism spectrum disorder. Cochrane Database Syst Rev 2017;11:CD011144.
31) **Parker KJ, Oztan O, Libove RA, Sumiyoshi RD, Jackson LP, Karhson DS, et al.** Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism. Proc Natl Acad Sci U S A 2017;114:8119-8124.
32) **Bernaerts S, Boets B, Bosmans G, Steyaert J, Alaerts K.** Behavioral effects of multiple-dose oxytocin treatment in autism: a randomized, placebo-controlled trial with long-term follow-up. Mol Autism 2020;11:6.
33) **Ooi YP, Weng SJ, Kossowsky J, Gerger H, Sung M.** Oxytocin and autism spectrum disorders: a systematic review and meta-analysis of randomized controlled trials. Pharmacopsychiatry 2017;50:5-13.
34) **Dean OM, Gray KM, Villagonzalo KA, Dodd S, Mohebbi M, Vick T, et al.** A randomised, double blind, placebo-controlled trial of a fixed dose of N-acetyl cysteine in children with autistic disorder. Aust N Z J Psychiatry 2017;51:241-249.
35) **Wink LK, Adams R, Wang Z, Klaunig JE, Plawecki MH, Posey DJ, et al.** A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. Mol Autism 2016; 7:26.
36) **Minshawi NF, Wink LK, Shaffer R, Plawecki MH, Posey DJ, Liu H, et al.** A randomized, placebo-controlled trial of D-cycloserine for the enhancement of social skills training in autism spectrum disorders. Mol Autism 2016;7:2.
37) **Aman MG, Findling RL, Hardan AY, Hendren RL, Melmed RD, Kehinde-Nelson O, et al.** Safety and efficacy of memantine in children with autism: randomized, placebo-controlled study and open-label extension. J Child Adolesc Psychopharmacol 2017;27:403-412.
38) **Centers for Disease Control and Prevention.** Autism spectrum disorder (ASD). Recommendations and guidelines [Internet]. Atlanta, GA: Centers for Disease Control and Prevention [cited 2021 Nov 20]. Available from: https://www.cdc.gov/ncbddd/autism/hcp-recommendations.html.
39) **Fombonne E, Goin-Kochel RP, O'Roak BJ; SPARK Consortium.** Beliefs in vaccine as causes of autism among SPARK cohort caregivers. Vaccine 2020;38:1794-1803.
40) **National Institute for Health and Care Excellence.** Autism: The management and support of children and young people on the autism spectrum: NICE guideline DRAFT [Internet]. London: National Institute for Health and Care Excellence [cited 2016 May 24]. Available from: https://www.nice.org.uk/guidance/cg170/documents/autism-management-of-autism-in-children-and-young-people-nice-version2.
41) **National Institute for Health and Care Excellence.** Autism spectrum disorder in adults: diagnosis and management [Internet]. London: National Institute for Health and Care Excellence [cited 2021 Nov 20]. Available from: https://www.nice.org.uk/guidance/cg142.
42) **Williams KJ, Wray JA, Wheeler DM.** Intravenous secretin for autism spectrum disorders (ASD). Cochrane Database Syst Rev 2012; 2012:CD003495.
43) **Wong HH, Smith RG.** Patterns of complementary and alternative medical therapy use in children diagnosed with autism spectrum disorders. J Autism Dev Disord 2006;36:901-909.
44) **Hyman SL, Levy SE.** Dietary, complementary and alternative therapies. In: Reichow B, Doehring P, Cicchetti DV, Volkmar FR, editors. Evidence-based practices and treatments for children with autism. 1st ed. New York: Springer;2011. p.275-293.
45) **Reichow B, Doehring P, Cicchetti DV, Volkmar FR.** Evidence-based practices and treatments for children with autism. 1st ed. New York: Springer;2011.