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Review Article

A Literature Review on Co-morbid Autism Spectrum Disorder and Substance Use Disorder

Satoshi TAMIYA[1,2], Hiroko MIZUMA[1], Ryou KATOU[1], Saeko NAGAO[1]
1 Kure Midorigaoka Hospital
2 Himeji City Center for the Disabled
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Abstract

Psychiatrists and other mental health professionals used to assume that the characteristics of autism spectrum disorder (ASD), such as poor social and communication skills and a tendency to avoid social situations and abide by rules, would be protective against substance use disorder (SUD), and that ASD cases co-morbid with SUD would be uncommon. However, these assumptions have recently been challenged in part due to the changes in defining ASD, resulting in more variability in its phenotypes. Recent cases of ASD do not match the typical characteristics; thus, it is necessary to re-examine ASD/SUD co-morbidity. For this purpose, we reviewed available literature on the prevalence of ASD/SUD co-morbidity, psycho-social aspects of substance use by individuals with ASD, and assessment and treatment issues. We reviewed 11 research papers on children and adolescents with ASD and 13 on adults with ASD. Our literature review suggested that the prevalence of ASD/SUD co-morbidity may be higher than previously thought, and that ASD as a risk factor for substance use may become more problematic as individuals make a transition into adulthood. One explanation for this heightened prevalence, as described in the reviewed literature on the psycho-social aspects of substance use by individuals with ASD, is high social demands exceeding the individuals' innate capacities. Such social demands may induce mental distress to which these individuals would be more vulnerable than the general population, and for whom

substance use would possibly function as self-medication for negative emotions and improved social functioning. Thus, in terms of SUD assessment and treatment for individuals with ASD, treating professionals should pay close attention to what role substance use plays in the lives of individuals with ASD. Previous studies found that nonabstinent reduction could be a reasonable option as a treatment goal for alcohol use disorder (AUD); however, we believe that this should be decided according to the AUD severity of each individual patient. In terms of therapeutic interventions, the characteristics of ASD should be taken into consideration. Less emphasis should be placed on the importance of group modality in favor of a more individual-oriented treatment modality, and utilization of more supportive and directive rather than insight-oriented approaches. Furthermore, social and vocational support to help structure the everyday lives of individuals with ASD would be beneficial in addition to SUD treatment. Because many of the reviewed research papers were published abroad, mostly in European and North-American countries, the differences in national policies and public attitudes on substance use necessitate mental health professionals in Japan conducting further research to apply these findings to Japanese ASD and SUD patients.

Keywords: autism spectrum disorder, substance use disorder, alcohol use disorder, co-morbidity

Introduction

Traditionally, the relationship between autism spectrum disorder (ASD), which is characterized by impaired interpersonal communication and imagination, and substance use disorder (SUD), which interferes with daily life due to substance use, has not been widely discussed. For example, in DSM-5 3), SUD is not listed as a co-morbidity of ASD, and conversely, ASD is not listed as a co-morbidity of alcohol use disorder (AUD) or any other SUD. There is no mention of ASD/SUD co-morbidity in textbooks on general psychiatry 57) or child and adolescent psychiatry 46)68). There is no entry of "alcohol" or "addiction" in the index to "Handbook of Autism and Pervasive Developmental Disorders" 71), nor is there any mention of ASD in international books on SUD treatment 8)23).

Although studies on ASD/SUD co-morbidity have been reported since the early 2000s, the descriptions have been rather brief. For example, a

monograph on Asperger's disorder published in 2000 30) stated only that adults with the disorder sometimes use alcohol or drugs to deal with anxiety, but that the frequency of such use is unknown (p.390). In the U.K., Berney, T. stated the following in a 2004 paper 7):

Alcohol is an effective tranquilliser, particularly for someone who finds social groups uncomfortable. Asperger syndrome can add a compulsive quality to social drinking and encourage isolated drinking ungoverned by normal societal conventions. The evidence for alcohol misuse in Asperger syndrome is more anecdotal than quantified by systematic research, but its significance lies in the quality of its psychopathology rather than in any increase in frequency of drinking. (p.346)

This is the only mention of alcohol consumption in the 11-page paper on Asperger's syndrome. However, this is an important point that will be discussed later.

In 2008, a monograph 69) by Tinsley, M. et al. was published in the UK. This is the first comprehensive work to focus on the relationship between ASD and AUD, and is interesting because it consists mostly of patients' narratives based on their own experiences. Tinsley, M., et al. described their book as "a tentative initial enquiry into a new area" (p.12).

Since around 2010, the number of articles related to ASD/SUD co-morbidity has increased. van Wijngaarden-Cremers, P.J.M. et al. 70) discussed the perceptual characteristics and social sensitivity of the two groups and identified neurobiological, evolutionary, genetic, and psychophysiological similarities. Furthermore, Rothwell, P.E. 55) discussed neurobiological similarities in two areas. One area was the overlapping neural circuits and neuromodulatory systems in the striatum and basal ganglia. The other overlapping area was FMRP and MECP2 involved in Fragile X syndrome and Rett syndrome, which exhibit ASD characteristics and are also involved in SUD addictive behaviors. Although not an academic book, an essay 52) by Regan, T., published in 2015, is interesting for its graphic description of her own internal experiences surrounding alcohol consumption. In parallel, a number of papers, which are presented below, were published, and in 2018, a monograph 37) was published in the United States, which can be considered a summary at this point in time. The latest issue of

JAMA Pediatrics (at the time of writing this article) published an editorial 4), entitled: "Autism spectrum disorder and the risk of substance use disorder: a call for targeted screening and prevention in adolescents".

Our Kure Midorigaoka Hospital specializes in alcoholism, but in recent years has also been focusing on the treatment of developmental disorders, encountering cases of ASD/SUD co-morbidity. These experiences motivated us to review the literature on this issue and to write this article. However, it is not a systematic review, as it is mainly based on the studies searched by keywords such as "autism" and "addiction" and their citations. The literature is limited to English or Japanese. Although most of the studies reviewed here are foreign literature, special attention is paid to AUDs in light of the relatively low prevalence of SUDs other than AUD in Japan.

I. Prevalence of ASD/AUD co-morbidity

Lalanne, L. et al. 38) reported two cases of high-functioning autistic adults in France, and explained the importance of identifying individuals with ASD among SUD patients. How often are ASD and SUD combined? The following are some of the reasons why ASD/SUD co-morbidities were conventionally assumed to be uncommon.

・Individuals with ASD tend to abide by rules 37) and do not use illegal drugs or drink to excess.

・Individuals with ASD cannot tolerate the sensation of drinking or drug use because of their sensory characteristics 37).

・Individuals with ASD tend to be isolated in interpersonal relationships and are not pressured by others to use illegal drugs or drink alcohol 6). They also do not participate in social gatherings that involve alcohol consumption.

・Individuals with ASD have poor social and communication skills and are not capable of bargaining to obtain illegal drugs 33).

However, as the definition of ASD has changed, variability in the phenotypes of individuals with ASD has been recognized, and the conventional image of ASD has been reconsidered. For example, individuals with ASD who pander to others due to immaturity of interpersonal skills are more susceptible to pressure 3)21). In the Netherlands, Sizoo, B.B. et al. 62) found that ASD individuals with concomitant SUD were less impaired in interpersonal skills than those

without SUD and had no difficulty in obtaining illegal drugs. Thus, the relationship between ASD and SUD is complex and varied, and Komoto et al. 31) stated that it is impossible to determine whether ASD characteristics are proactive or preventive with regard to SUD. In addition, as efforts have been made to support ASD in the medical, educational, and welfare fields in recent years, inclusion and integration have progressed, and many individuals with ASD attend regular schools and live in society together with individuals with typical development. Individuals with ASD who have inadequate interpersonal skills are exposed to many risks as a result, and this includes a risk of SUD 37). In particular, a gap in support occurs during the transition period from childhood/adolescence to adulthood, and serious risks exist here 72). Reports on the prevalence of ASD/SUD co-morbidity have been increasing against this background, and several review articles have been published.

In Norway, Arnevik, E.A. et al. 5) reviewed 18 reports and found that the rates of SUD co-morbidity were generally lower in individuals with ASD than in individuals with typical development, but the difference was not statistically significant in all the reviewed studies. They also stated that the prevalence of co-morbidities may increase when intellectual ability is relatively high.

In the U.S., Rosen, T.E. et al. 54) looked at the overall co-morbidities of ASD, and also mentioned SUD co-morbidity, stating that the SUD co-morbidity rate in individuals with ASD was higher than that in the general population, but lower than that in patients with other mental disorders. They also pointed out that attention-deficit/hyperactivity disorder (ADHD) co-morbidity should be taken into account when considering co-morbidities of ASD.

In Spain, Lugo-Marín, J. et al. 41) conducted a review and meta-analysis of the literature on co-morbidities in adults with ASD, including 16 reports on SUD. The SUD co-morbidity rate was 8.3%, which was as low as that of eating disorder as a co-morbidity of ASD. Alcohol was the most common substance used, followed by cannabis, and the rate of using other substances was low. However, caution is warranted in interpreting these results because several studies included a small number of special samples, such as adults with ASD with suicide-related problems 50).

In Canada, Ressel, M. et al. 53) qualitatively evaluated 26 reports on ASD and substance use, and reported

SUD co-morbidity rates ranging from 1.3 to 36%, which is higher than previously thought. Tobacco, alcohol, and cannabis were the most frequently used drugs, in that order. The AUD co-morbidity rate was lower in patients with intellectual disability (ID).

A review of various reports indicated that the co-morbidity of ID and ADHD is a factor that influences the ASD/SUD co-morbidity rate 16), and some reports indicate that the co-morbidity rate varies with age. In this article, we review studies including those published after the above four reports, looking at childhood/adolescence and adulthood separately and paying special attention to ID and/or ADHD comorbidities. Because studies with different samples cannot be treated equally, epidemiological studies of the general population and clinical studies of patients are reviewed separately as well, and presented mostly in the order of publication (Table). There were also reports 12)17)65)66) on individuals with ASD who have been involved in legal matters: we do not cover them here because they are a special population.

1. Childhood and adolescence

Six epidemiological studies are presented here. In the U.S., Brookman-Frazee, L. et al. 9) examined children and adolescents receiving support in five systems (mental health, special education, child welfare, juvenile justice, and substance use) and reported on 1,603 cases (age: 6-19 years) including 42 ASD cases and 178 ID cases. Only 1.3% of ASD/ID children received support in substance use-related facilities, being lower than the 3.8% of non-ASD/ID children (odds ratio: 0.5). However, ASD and ID were not examined separately.

In Denmark, Abdallah, M.W. et al. 1) examined co-morbid psychiatric disorders in 414 children with ASD (mean age: 16.28 years). A total of 0.7% (three cases) of the ASD group had alcohol-related disorders, which was lower than 1.3% in the non-ASD control group, but the difference was not statistically significant. Co-morbidity with ID had no impact.

In the United States, Mulligan, R.C. et al. 47) studied 2,937 adolescents (age: 13-17 years) without diagnosed autism or ID who grew up in families with four or more children. The odds ratio of alcohol use was 1.06 for those with high levels of autistic traits but no ADHD co-morbidity, whereas it was 2.44 for those with ADHD, a statistically significant increase. On the other hand, substance use other than alcohol and tobacco use was

significantly correlated with autistic traits regardless of ADHD co-morbidity. Mulligan et al. concluded, “it should not be assumed that adolescents with mild to moderate ASD have a low risk of SU (substance use), especially if ADHD is also present” (p.86).

Kerns, C.M. et al. 27) examined the mental health of 1,131 ASD children (16.8% with ID) based on a U.S. survey of parents of children aged 3-17 years. When substance abuse was examined only for those aged 6-17 years, a total of 0.01% had a positive history, being significantly lower than 0.2% in non-ASD controls. However, depression and behavior/conduct problems were more prevalent than in the non-ASD control group, suggesting that ASD children may be at an increased risk of substance abuse later in life.

Similarly, Kaltenegger, H.C. et al. 26) from Sweden, who examined risk drinking in adolescents and young adults, also noted an association with age. In this report, twins were included in a longitudinal study at ages 15, 18, and 24 years. Totals of 3.60%, 9.20%, and 13.25% of ASD individuals showed harmful/hazardous alcohol use at ages 15, 18, and 24 years, respectively. These figures were lower than those of non-ASD controls at all ages, but the rate increased with age. Kaltenegger et al. concluded, "the prevalence of risk drinking in ASD was lower than in individuals without ASD, yet increasing continuously with age.” The risk tended to increase with co-existing ADHD and LD (Learning Disorder).

Huang, J.S. et al. 20) reported on 6,599 Taiwanese children with ASD (mean age: 11.9 years). The hazard ratios for SUD, AUD, and drug use disorder were 2.33, 2.07, and 3.00, respectively, all being significantly higher than those in non-ASD controls. The AUD co-morbidity rate was particularly high when ID, ADHD, and anxiety disorders co-existed. Furthermore, the mortality rate of ASD children with SUD was significantly higher than that of non-SUD/non-ASD children (hazard ratio: 3.17). Therefore, it was concluded that children with ASD should be carefully monitored for developing SUDs.

Four clinical studies are listed below. In the U.S., Mandell, D.S. et al. 43) examined the characteristics of 124 children with ASD receiving psychiatric care. They included 48 children with autistic disorder (mean age: 7.9 years) and 76 children with Asperger's disorder (mean age: 8.6 years). No child with ASD was referred for substance abuse as the

primary presenting problem. The rate of substance use among ASD children was 6.3% for children with autistic disorder and 2.7% for children with Asperger's disorder, which was significantly lower (odds ratio: 0.18) than the rate of use among children with other diagnoses (21.3%) for ASD as a whole.

In the U.K., Santosh, P.J. et al. 58) included 97 adolescents (mean age: 14.27 years) with ASD (pervasive developmental disorder in the original paper). Of these, 38 (39.2%) were co-morbid with ID. The rate of substance use among adolescents with ASD was 3.1% (3 cases), which was significantly lower than 16.7% among controls with other psychiatric disorders. All three patients had no ID co-morbidities, and when only 59 patients without ID co-morbidities were considered, the substance use rate was 5.1%. Santosh et al. concluded that low IQ can only partially explain the difference in substance uses between the ASD group and psychiatric controls. All three patients had ADHD.

In the U.S., Joshi, G. et al. 24) reviewed the co-morbid psychiatric disorders of 217 children and adolescents with ASD (3-17 years old, mean: 9.7 years) who were referred to a pediatric psychopharmacology program. One child had SUD, being significantly less frequent than in non-ASD controls. The ADHD co-morbidity rate in children with ASD was 83%. The participants' intellectual ability was not objectively assessed.

Mangerud, W.L. et al. 45) examined substance use among adolescents (mean age: 15.68 years) receiving psychiatric treatment in Norway. Cases with poor "cognitive function" were excluded. Of 39 ASD patients, 3 (7.7%) had a history of alcohol use, the lowest among the psychiatric disorders studied. No ASD adolescent had a history of smoking or drug use.

2. Adulthood

Five epidemiological studies are presented below. A twin study by Lundström, S. et al. 42) in Sweden examined the association between ASD characteristics and mental health problems in children and adults, and only 18,349 adults were included with regard to substance abuse. The results showed that the odds ratio (5.7) of substance abuse co-morbidities was higher among those with ASD. However, ID co-morbidities were not strictly controlled.

De Alwis, D. et al.11) reported an Australian study of substance use in 3,080 subjects (age: 27-40 years). The rate of drinking to intoxication

decreased with higher ASD traits, while the rate of alcohol dependence increased. ADHD symptoms were not correlated with the rate of drinking to intoxication, but were positively correlated with the rate of alcohol dependence.

In Sweden, Butwicka, A. et al. 10) examined substance use in 26,986 individuals with ASD and found that ASD could be a risk factor for SUD. Specifically, 3.6% had SUD, being significantly higher than 0.8% in non-ASD controls; AUD was also present in 2.1% of ASD individuals, being significantly higher than 0.6% in non-ASD controls; ID co-morbidities did not increase SUD incidence, and ADHD co-morbidities did not affect substance use.

In Canada, Weiss, J. A. et al. 72) compared the health profiles of 5,095 young adults with ASD (age: 18-24 years) with other developmental and non-developmental disorder groups. They found that the SUD co-morbidity rate in the ASD group was lower than that in the other developmental disorder group (odds ratio: 0.74), but higher than that in the non-developmental disorder group (odds ratio 1.58). This suggests that the support gap during the transition from childhood/adolescence to adulthood should be noted.

In Sweden, Nylander, L. et al. 48) focused on the elderly. In this report, they examined the co-morbid psychiatric disorders and service use of 601 ASD patients aged 55-96 years. A total of 57% had ID co-morbidity and 4% had ADHD co-morbidity. Although specific figures were not given, SUD was a complicating psychiatric disorder in a few percent of the patients, and most patients did not have ID. The number of visits to a psychiatric clinic for substance dependency treatment was 117 (8%), all of which were by patients with Asperger syndrome.

Nine clinical studies are presented below. In the Netherlands, Ketelaars, C. et al. 28) examined co-morbid psychiatric disorders in 15 adults (age: 18-24.5 years) diagnosed with "mild ASD" without ID. Individual diagnoses included 10 cases of pervasive developmental disorder not otherwise specified, four cases of Asperger's disorder, and one case of high-functioning autism. Substance abuse did not differ significantly from non-ASD control group. This was a pilot study of a small number of "mild ASD" cases, so it is difficult to generalize the results.

Hofvander, B. et al.19) recruited 122 ASD individuals with normal intelligence (mean age: 29 years) in France and Sweden to examine the

co-morbidity rate of psychiatric disorders. They found that 19 (16%) had SUDs, and discussed that SUDs were not common among individuals with ASD. Alcohol was the most common substance used by 15 individuals, followed by cannabis in four. Fifty-two individuals (43%) had ADHD, and four had antisocial personality disorder.

In a study by Sizoo et al. 63) of 70 ASD patients (mean age: 34 years) without ID co-morbidities, the SUD co-morbidity rate, including gambling addiction, was compared with that of 53 ADHD adults. The ASD/SUD co-morbidity rate of 30% was significantly lower than that of 58% in ADHD adults, but did not differ from the SUD co-morbidity rate in those with other psychiatric disorders. When restricted to AUD, ASD (14%) and ADHD (13%) were comparable. Sizoo et al. concluded that ASD patients are at risk for developing SUDs.

In Sweden, Lugnegård, T. et al. 40) investigated the co-morbidities of psychiatric disorders in 54 young adults (mean age: 27 years) with Asperger disorder. There were no cases co-morbid with ID. The rate of substance dependence was 11% (4 alcohol, 4 drugs), which was lower than the rate of other psychiatric disorders. The authors discussed that this result could be explained in large part by ADHD co-morbidities.

In the U.S., Mandell et al. 44) studied patients civilly committed to a state psychiatric hospital for a long period of time (average: 17.6 years). Of 141 inpatients (mean age: 52.0 years), 14 (9.9%) had ASD, and nine (64.3%) of them had co-morbid ID. A history of substance use or abuse was present in five (35.7%) of the ASD group, being significantly less prevalent than 78.7% in the non-ASD control group.

In the Netherlands, van Wijngaarden-Cremers et al. 70) found eight (6.7%) cases with co-morbid ASD among 118 adults with SUD, and reported that the ASD co-morbidity rate was higher than 1% in the general population. Eight patients, including four AUD patients, had no ID co-morbidities.

In Germany, Roy, M. et al. 56) examined co-morbid psychiatric disorders in 50 adults (age: 20-62 years) with Asperger disorder without ID. Alcohol abuse was noted in five (10%) and alcohol dependence in four (8%). Alcohol abuse/dependence was more common in males, and all dependence cases were over 40 years of age. According to this report, the prevalence of alcohol dependence in the general German population was 6.3%, and the

authors concluded, “alcohol abuse and dependence should be noted in adults with AS (Asperger disorder)” (p.56). Cannabis abuse was observed in six patients (12%), but no drug dependence other than alcohol was observed.

In the U.S., Fortuna, R.J. et al. 13) examined the health conditions and functional status of 255 individuals with ASD (age: 18-71 years). Fortuna et al. defined alcohol misuse as four or more drinks almost every day. The intelligence quotient was known in 141 individuals (55.3%), 128 of whom had concomitant ID. A unique feature of this report is that the variables were examined by age group. The ADHD co-morbidity rates varied by age group, with 27.6% in the 18-29 age group, 9.0% in the 30-39 age group, and 2.8% in the 40+ age group. However, smoking and alcohol misuse rates were significantly lower in all age groups than in the general population.

In the Netherlands, Lever, A. G. et al. 39) examined 172 ASD individuals without ID by age group for co-morbid psychiatric disorders. The SUD co-morbidity rates were 19.6 and 33.3% in the younger age group (19-38 years), 10.6 and 19.6% in the middle age group (39-54 years), 17.8 and 21.9% in the older age group (55-79 years), and 15.9% and 25.3% in all age groups, respectively, in ASD individuals and the general population. The overall SUD co-morbidity rate was significantly lower in people with ASD. However, the SUD co-morbidity rates in the general population control group in this report were higher than those in previous studies.

3. Summary of co-morbidity prevalence

As can be seen from the above overview, the question of whether ASD/AUD co-morbidities are more or less common is not a simple one. The association between ASD and AUD is complicated by factors such as age, intellectual level, and other co-morbidities. The trend is that the SUD co-morbidity rate in ASD is higher in patients with ADHD and lower in those with ID. It is well-known that ADHD and SUD are frequently co-morbid, and it is not surprising that the prevalence of SUD is also increased in individuals with ASD due to co-existing ADHD. However, among the studies reviewed here, there are reports of a high prevalence of SUDs in individuals with ASD when ADHD and other co-morbidities are controlled for 10)20). We believe that SUDs in individuals with ASD are not solely explained by co-morbidities such as ADHD.

Many reports indicate that the SUD co-morbidity rate is higher in adulthood than in childhood/adolescence. One possible reason is as follows: Children with ASD may have less experience with alcohol and drugs than children with typical development because of their tendency to follow the rules, as has been conventionally believed. However, once they reach the age of adulthood, the rate of consumption and incidence of use disorder may increase for some reason, especially with regard to alcohol, partly because it is legal. The transition to adulthood may be the turning point 72).

Therefore, it is important to consider the risk factors of SUD in individuals with ASD, rather than focusing only on the prevalence of co-morbidities. This is the reason why Berney 7) pointed out that the significance of SUD in ASD "lies in the quality of its psychopathology rather than in any increase in frequency of drinking" (p.346). In the next section, we will review the literature on the implications of alcohol consumption for individuals with ASD. From here, the discussion will focus on alcohol consumption and AUD in light of the aforementioned current situation in Japan.

II. Psycho-social aspects related to alcohol consumption in individuals with ASD

1. Psychology of drinking in individuals with ASD

When individuals with ASD drink alcohol, is it related to their ASD characteristics? Individuals with ASD, who often have poor interpersonal skills, are more likely to experience increased anxiety and have a higher rate of anxiety disorders 39)54). As mentioned earlier, Berney 7) pointed out that alcohol can be a tranquilizer for coping with anxiety in individuals with ASD, but no specific data have been presented.

Empirical data were published later. Tinsley 69) stated in detail, based on his own experience, that people with ASD drink alcohol as a means of relieving interpersonal tension. He wrote that people with ASD "drink for the same reasons as many other problem drinkers and alcoholics, but with a different degree of necessity" (p.21). In the Netherlands, Kronenberg, L.M. et al. 34) examined 31 adults with ASD/SUD co-morbidities (intelligence quotient ≧ 80), reporting that alcohol consumption facilitated interpersonal interactions in individuals with ASD, and other reports 70) made the same point. Two cases reported by Lalanne,

L. et al. 38) showed that patients drank to cope with anxiety caused by unexpected events, sensory overload, and interpersonal situations, and to improve their interpersonal skills. In Russia, Jargin, S.V. 22) reported a case that was probably his own experience, and described how a person with ASD tried to overcome communication difficulties by drinking. In the U.S., Abello, L.S. 2) conducted a meta-analysis of the literature and found that individuals with ASD drink to enhance their interpersonal skills. Four patients with ASD/SUD in a study by Helverschou, S.B. et al. 18) gave reasons for substance use: to reduce anxiety and improve social skills and concentration; to become able to socialize; to forget problems; and to get peace of mind. Regan 52), mentioned earlier, described her experience of drinking for the first time at the age of 13, as follows:

The bitter magic seemed to grease the squeaky and rusty cogs and wheels in my head. Things ran smoothly. Things got quieter. Things in the world seemed more approachable and real. Less like the fragile, sensory-imploding world that went unchallenged when dry and sober. (p.13)

Thus, alcohol for ASD individuals is often so-called self-medication 18)21)37). Therefore, conversely, Lalanne et al. 38) pointed out that the behavior of ASD individuals who drink is close to "normal" and that SUD in ASD individuals is difficult to notice. Tinsley et al. 69) also stated that alcohol is a means of becoming "normal".

Ressel et al. 53) discussed the "expectancy hypothesis" of Brown, S. A. This hypothesis states that "the fulfillment of specific expectations that an individual holds regarding a substance leads to its increased and continued use" (p.914). In other words, psychological factors that lead to the expectation of the substance's efficacy, apart from its actual effect as a self-medication, work to reinforce substance use. It is possible that this psychological factor plays a role in the drinking of individuals with ASD.

Although not in the academic literature, Gerland, G. 15), an ASD individual, stated another reason for substance use, as follows:

Hashish was a good way for me to cover up various things I wasn't good at. … "I smoked that, and this is what happened." It's really quite clear, isn't it? (p.178-179, back-translated from the Japanese edition)

In other words: the use of cannabis to rationalize one's own weaknesses. In a different sense from self-medication, it is a means of coping with one's own ASD characteristics. This is also true for alcohol consumption.

A study on personality traits has been reported. In Spain, Ramos, M. et al. 51) examined the correlation between personality traits and risk of drug use in 26 adolescents with Asperger's disorder without intellectual problems, and found that introversive, inhibited, doleful, and borderline personality traits may be risks for substance use.

2. Sensory perception of drinking in individuals with ASD

King, A. et al. 29) introduced the "incentive-sensitization theory" of AUD and argued that it is necessary to look at the relationship with sensory characteristics of ASD. According to this theory, the reason AUD individuals continue to drink is not because of the tolerance that develops with chronic drinking, but because their subjective experience of drinking changes over time, causing them to seek alcohol more. In individuals with ASD who have unique sensory characteristics, these sensations may play a role in the development of AUD.

Komoto et al. 31) found that in the "autism type," "the sensation of intoxication caused by the pharmacological effects of alcohol itself is the main driving force of drinking behavior." They also pointed out that "abnormal drunkenness tends to occur more frequently, and explosive deviant behavior is more likely to occur" (p.465, quotations translated from the Japanese texts).

3. Social factors of drinking in individuals with ASD

Although few reports have examined the social factors of alcohol consumption in individuals with ASD, we present the following descriptions related to social factors in various reports because this is a topic that needs further investigation.

When ASD is diagnosed in childhood, the involvement of parents and guardians has a significant impact on the child's living environment. Kaltenegger et al. 26), who analyzed data from a longitudinal twin study, pointed out that "(p)arents of children with ASD face an increased subjective and objective caregiving burden, including for instance greater need for vigilant parenting and monitoring" (p.3). Also, Santosh et al. 58), who examined adolescents with pervasive developmental disorders aged 12 to 18 years, found higher

rates of substance use (odds ratio: 1.44) when parental supervision or control was inadequate.

Regardless of age, interpersonal relationships are also a social factor that cannot be ignored; Ramos et al. 51) suggest this point. In their study, 26 adolescents with Asperger's syndrome felt that their friends had negative attitudes toward substance use and tended to be non-users. They themselves often tried to refrain from engaging in risky activities such as going to places where substances were used. These were all protective factors against drug use. On the other hand, they often felt difficulties in family relationships, school life, and leisure activities, and these factors might increase the risk of drug use.

4. Summary of psycho-social factors

The purpose of drinking alcohol among individuals with ASD is to relieve anxiety in interpersonal situations and sensory overload, which is closely related to ASD characteristics. It is considered to be self-medication as a way to cope with the stressors of social life. Of course, individuals with typical development also experience similar mental distress, but it is more difficult for individuals with ASD to tolerate 37). Therefore, ASD characteristics may become apparent during adolescence, when social demands increase 7), and the risk of substance use also increases during the transition from adolescence to adulthood 56).

Again, the issue of ADHD co-morbidities should be mentioned. Sizoo et al. 61), who examined the temperament and character profiles of ASD/SUD and ADHD/SUD individuals, noted that the personality characteristics of the two groups were different. That is, the former had a low tendency toward reward dependence and a high tendency toward harm avoidance, while the latter had a high tendency toward novelty seeking. It is possible that this difference affects substance use. Kronenberg et al. noted differences in everyday life consequences of substance use 32) and coping styles 34) between the two groups. For example, they found that substance use in ADHD patients could improve hyperactivity, while substance use in ASD patients could suppress the jumble of thoughts and emotions, help them relax and get through the day, and help them escape feelings of pure boredom. Thus, even with regard to qualitative aspects, substance use in ASD individuals may not be explained solely by ADHD co-morbidities.

In this regard, it is undeniable that ASD characteristics themselves can

be a risk factor for AUD. This is an essential perspective when considering the assessment and treatment of individuals with ASD/AUD co-morbidities.

III. Assessment and treatment of individuals with ASD/AUD co-morbidities

1. Assessment

Since there is a paucity of literature on the assessment of individuals with ASD/AUD co-morbidities, we will present some of the points raised in discussions of various reports.

First, we would like to address the importance of ASD diagnosis. Two reports 35)38) pointed out that ASD characteristics are sometimes first noted during SUD treatment. One of the patients reported by Lalanne et al. 38) was diagnosed with ASD after starting SUD treatment, and was able to maintain moderation in drinking while continuing SUD treatment as a result of a revised treatment plan in accordance with ASD characteristics. Naturally, support is not possible without recognition of ASD characteristics. Ressel et al. 53) pointed out that a delay in ASD diagnosis is an SUD risk. It cannot be overemphasized that the possibility of ASD should always be kept in mind when supporting SUD individuals 67)69).

Conversely, it is also necessary to keep SUD in mind in the treatment of ASD. In particular, SUD screening should be performed in the treatment of adolescents and adults 37). However, according to Ressel et al. 53), there is no substance abuse assessment or screening method specifically for ASD cases, and this is an issue for the future. Fortuna et al. 13) found that health care providers treating individuals with ASD tended not to ask about substance use. In the treatment of individuals with ASD, who often have communication difficulties, health care providers need to explicitly ask about substance use 21). In addition, it is important to note that preconceived notions about ASD, as described at the beginning of this paper, are also a factor that makes assessment difficult 13).

As mentioned earlier, co-morbidities of ADHD and ID are associated with SUD and should be evaluated with particular care. But the evaluation of ADHD and ID that are co-morbid with ASD and SUD involves specific difficulties 37). For example, Sizoo et al. 62) reported that it is difficult to differentiate ASD and ADHD persons with concomitant SUD by the Autism-Spectrum Quotient (AQ). In this report, the social skills of individuals with ASD co-morbid with SUD were superior to those of individuals with

ASD without SUD. This led Sizoo et al. to state that "when there is comorbidity with SUD the clinician should be cautious; in that case the total AQ score in patients with ASD can be attenuated by a lower score on the Social skills subscale" (p. 1,295).

2. Treatment goals

The conventional treatment goal for AUD has been abstinence from alcohol. However, this trend has been changing recently. A report 60) on drinking trends among the general American population found that the rate of alcohol consumption has been increasing in recent years, and pointed out that "non-abstinent drinking reduction … leads to significant physical, psychological, and emotional improvement" (p.10) in the clinical treatment of problem drinking. Nalmefene, a " medicine to reduce alcohol consumption," was approved and marketed in Japan in 2019. How should treatment goals be set for patients with ASD/AUD?

In the literature, too, different goal setting from conventional AUD treatment has been proposed in consideration of the ASD characteristics mentioned above. Kronenberg et al. 34) stated, "patients with SUD+ASD often only want to reduce their drinking, because it can *facilitate* their social interaction" (p.8, original italics). They then recommend controlled substance use as a treatment goal for AUD patients with ASD 35), using the personal recovery concept of Slade, M. et al. 64). Personal recovery is a concept that emphasizes the patient's own subjective treatment goals, as opposed to the conventional concept of clinical recovery, which aims to improve symptoms of the disease. When based on this concept, abstinence is not the only goal of treatment. It has been pointed out that ASD patients who adhere to their "own style" find it easier to discover their own controlled drinking techniques rather than to be forced to abstain from alcohol altogether 18)37). Furthermore, there is a report 35) that ASD patients who have completely abstained from alcohol feel a decline in social functioning. Thus, nonabstinent reduction has been proposed as a realistic treatment goal.

3. Treatment techniques

Some aspects of conventional AUD treatment are not suitable for individuals with ASD 5)18)21). For example, group modality such as AA (Alcoholics Anonymous) and *danshu-kai* (traditional self-help groups for alcoholics in Japan) has been emphasized. However, individuals

with ASD, who often have poor interpersonal skills, find group settings uncomfortable 5)21)31)70). Furthermore, AA is based on religious ideology, and the relationship with "God" is discussed, but this kind of abstract concept is difficult for individuals with ASD to understand 37)69). The equivalent in *danshu-kai* is the relationship with "senior group members," which may also be confusing to individuals with ASD who have difficulty feeling emotional connections with others. Considering the above, it may be better to focus on individual therapy in the treatment of AUD co-morbid with ASD.

In addition, it is not easy to envision new situations due to ASD characteristics that make it difficult to understand abstract concepts. This is one of the reasons why advice such as, "If you keep drinking, it will kill you," does not work 69). Therefore, directive psychotherapy with concrete instructions may be more effective than insight-oriented psychotherapy 18)35). In behavioral therapy, more direct and tangible reinforcers may be useful 21). Since ASD individuals may lack common-sense knowledge, the illegality of drug use also needs to be reaffirmed 21).

Although few in number, a variety of treatment methods are reported. Helverschou et al. 18) reported four ASD/SUD patients treated with cognitive behavioral therapy. All were male and had an IQ of 70 or higher. Two patients achieved abstinence from drugs and alcohol, one patient maintained reduced use, and one patient continued to drink. Kaltenegger et al. 25) used mentalization as a treatment for SUD patients with subclinical autistic traits and borderline personality disorder. In this study, the more pronounced the autistic traits, the significantly greater the number of drinking days after treatment.

Regardless of which treatment technique is used, coping strategies for anxiety is necessary for individuals with ASD who drink to reduce anxiety 69). Opportunities for participation in social activities and learning how to behave in such participation are also important 32).

AUD treatment alone is not sufficient in cases with ASD/AUD co-morbidities 35). Since social adaptation is often difficult due to ASD characteristics, lifestyle and vocational support should also be considered. Based on an interview survey of SUD adults co-morbid with ASD (12 cases) or ADHD (11 cases), Kronenberg et al. 32) found that substance use improves daily difficulties in the short term but leads to a vicious cycle that develops into

serious problems in the long term. Ressel et al. 53) also cited a lack of social support and delay in ASD diagnosis as risk factors for substance use or SUD co-morbidities in individuals with ASD, and stated that "a vicious cycle may ensue wherein substance use contributes to further lack of structure creating more difficulties with organization" (p. 914). Other reports 18) made similar points.

In addition to early education on substance use, support during the transition from adolescence to adulthood is crucial for SUD prevention 72). Kunreuther, E. et al. 37) underscored the need for assistance after entering college. The seamless help emphasized in ASD support will be beneficial for SUDs as well.

4. Prognosis

Tabata, K. et al. 67) presented three cases and reported that ASD patients with strong preferences, obsessive-compulsive behaviors, and stereotypies were more likely to be able to maintain abstinence from alcohol with treatment. Komoto et al. 31) also found that overselectivity, an ASD trait, drives abstinence by incorporating the "recovery process" and "image of the sober person" on an intellectual level (overselectivity refers to a conscious focus of attention, sometimes called "single focus").

Sizoo et al. 61), who examined 75 ASD adults without ID, reported that those with-co-morbid SUD had higher social orientation than those without SUD, and associated this with the "paradox of the dually diagnosed" 49). This concept was proposed in relation to the association between SUD and schizophrenia, in which schizophrenic patients with SUD were behaviorally more disorganized but more socially competent than schizophrenic patients without SUD. If this is the case for ASD, it may be easier to keep abstinence due to relatively higher-level social skills. However, this is only in comparison with ASD individuals without SUD, and there is still a need to provide support to cope with the difficulties in social life associated with ASD characteristics.

5. Summary of assessment and treatment

The conventional therapeutic framework of AUD is not sufficient for the treatment of individuals with ASD/AUD. It has been argued that it is necessary to develop a treatment plan that takes into account the quality of psychopathology 7) derived from ASD characteristics, such as emphasizing an individual approach rather than group modality and

targeting nonabstinent reduction rather than complete abstinence from alcohol. Furthermore, we must not forget to provide not only SUD treatment but also general life support, such as lifestyle and vocational support. For this purpose, an understanding of ASD characteristics is required of SUD therapists 18).

IV. Overall Discussion

This paper is not a systematic review since the literature presented here is limited to what the authors were able to identify and obtain. Therefore, the possibility of selection bias of references cannot be ruled out.

Compared with reports on the prevalence of ASD/SUD co-morbidity, there are fewer reports on the substance use psychology of ASD individuals and AUD treatment. Studies on co-morbidity prevalence also vary in their methods and subjects. In addition, some studies have focused on normal drinking and substance use that does not reach the level of impairment, while others have focused on SUDs, which, strictly speaking, should be distinguished. Moreover, very few reports have examined drug use (disorders) other than alcohol by drug type. The issue of ASD/SUD co-morbidity is an area that is expected to be explored further in the future.

In summary, it is important to consider ASD characteristics in the treatment and support of patients with ASD/SUD co-morbidities. If the SUD co-morbidity prevalence is higher in adulthood than in childhood/adolescence, this may be due to the protective effect of the tendency to abide by rules, an ASD characteristic, since illegal drug use and underage drinking are prohibited by law. On the other hand, with regard to alcohol, it is legal to drink after reaching the age of adulthood, and individuals may resort to drinking to relieve the mental distress they experience in social life and become stuck in their drinking habits due to a lack of other coping skills. It has been suggested, therefore, that aiming for nonabstinent reduction rather than complete abstinence from alcohol may alleviate anxiety and tension in social situations and facilitate social life.

However, considering that AUD is a disease in which alcohol consumption is inherently uncontrollable, appropriateness of nonabstinent reduction as a treatment goal should be judged with caution. The recently published "New Guidelines for the Diagnosis and Treatment of Alcohol and Drug Use Disorders" in Japan 59)

clearly states that the goal of treatment should be abstinence from alcohol. We believe that appropriate treatment goals should be set according to the severity of each case and that nonabstinent reduction should not be uniformly recommended for individuals with ASD/AUD. Fukumoto 14), who examined ASD psychoanalytically, states that "in reality, nobody consists only of AS (autistic spectrum) structure; everyone also has parts of the structure with normal neurotic conflict and personality functioning," and that "these parts usually function as a 'false self' and may cause compensatory failure during maladjustment" (p. 901, quotations translated from the Japanese texts). Drinking alcohol can be said to merely support this "false self." In any case, we would like to re-emphasize the importance of setting up an appropriate treatment plan that takes ASD psychology into consideration.

Conclusion

In addition to the reports presented here, there are other studies that investigated the need for care and life satisfaction of adults with ASD/SUD co-morbidities 33) and the burden on the caregivers 36). As can be seen from an overview of the reports presented in this paper, many of them are from European and North-American countries, and their findings are not necessarily generalizable to other regions. In particular, there are regional differences in drinking habits and policies and public attitudes on substance use, so unique approaches in Japan are needed. We hope that this issue, which is a matter of global concern, will continue to attract further attention.

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Note: The following article, which is closely related to this paper, was published after this paper was accepted. We add it here for the readers' information.

Weir, E., Allison, C., Baron-Cohen, S.: Understanding the substance use of autistic adolescents and adults: a mixed-methods approach. Lancet Psychiatry, 8 (8); 673-685, 2021

Table　Prevalence of Autism Spectrum Disorder and Substance Use Disorder Co-morbidity

	Design	Authors	Subjects	Co-morbidity	Comment
Childhood/Adolescence	Epidemiological	Brookman-Frazee et al.[9]	1,603 involved in multiple public service systems (6-19y), including 42 with ASD and 178 with ID	1.3% of ASD/ID supported in substance use-related facilities	Lower than 3.8% of non-ASD/ID (OR: 0.5)
		Abdallah et al.[1]	414 ASD (MA: 16.28y) 820 non-ASD (MA: 16.26y)	0.7% of ASD co-morbid with alcohol-related disorders	NS (1.3% in non-ASD)
		Mulligan et al.[47]	2.937 without ID/autism in families with ≧4 children (13-17y)	OR 1.06 for alcohol use with high autistic traits	Alcohol use risk not high unless complicated with ADHD
		Kerns et al.[27]	42,283 (3-17y), including 1.131 ASD	0.01% of 6-17y positive for substance abuse history	Lower than 0.2% of non-ASD
		Kaltenegger et al.[26]	Twins in a longitudinal study: 10,050 at 15y, 7,931 at 18y, 2,882 at 24y	Harmful/hazardous alcohol use in ASD: 3.60% at 15y, 9.20% at 18y, 13.25% at 24%	Lower than non-ASD, but increases with age
		Huang et al.[20]	6,559 ASD (MA: 11.9y) 26,396 non-ASD (MA: 12.1y)	Hazard ratios: SUD 2.33, AUD 2.07, drug use disorder 3.00	Higher than non-ASD
	Clinical	Mandell et al.[43]	48 autistic disorder (MA: 7.9y) 76 Asperger's disorder (MA: 8.6y) 6.577 other diagnoses (MA: 11.5y)	Substance use: 6.3% in autistic disorder, 2.7% in Asperger's disorder	Lower than 21.3% of other diagnoses (OR: 0.18)
		Santosh et al.[58]	97 ASD (MA: 14.27y) 1.387 other diagnoses (MA: 14.36y)	Substance use: 3.1% in ASD	Lower than 16.7% among controls
		Joshi et al.[24]	217 ASD (MA: 9.7y) 217 non-ASD (MA: 10.9y)	1 SUD in ASD	Less frequent than 13 in non-ASD
		Mangerud et al.[45]	566 in psychiatric treatment (MA: 15.68y), including 39 ASD	Alcohol use: 7.7% in ASD	Lowest among psychiatric disorders studied

Adulthood	Epidemiological	Lundström et al.[42]	18,349 twins, including 68 ASD	OR 5.7 for substance abuse in ASD	Higher substance abuse
		De Alwis et al.[11]	3,080 twins (27-40y)	OR 1.42 for alcohol dependence if ASD traits high	Elevated risk for alcohol dependence if ASD traits high
		Butwicka et al.[10]	26,986 ASD 96,557 non-ASD	SUD: 3.6% in ASD	Higher than 0.8% in non-ASD
		Weiss et al.[72]	5.095 ASD 10,487 other developmental disorder 393,263 non-developmental disorder (all groups 18-24y)	OR for SUD 0.74 and 1.58, compared to other developmental disorder and non-developmental disorder, respectively	Lower than other developmental disorder, but higher than non-developmental disorder
		Nylander et al.[48]	601 ASD (55-96y)	A few percent had SUD	SUD uncommon
	Clinical	Ketelaars et al.[28]	15 with "mild ASD" without ID (18-24.5y) 21 non-ASD (18-55.9y)	Substance abuse: 20% in ASD	NS (10% in non-ASD)
		Hofvander et al.[19]	122 ASD with normal intelligence (MA: 29y)	SUD: 16%	SUD not common
		Sizoo et al.[63]	70 ASD without ID (MA: 34y)	SUD: 30%, AUD: 14%	ASD at risk for SUD
		Lugnegård et al.[40]	54 Asperger syndrome (MA: 27y)	Substance dependence: 11%	SUD uncommon
		Mandell et al.[44]	141 long-term inpatients (MA: 52.0y), including 14 ASD	Substance use/abuse: 35.7%	Lower than 78.7% in non-ASD
		van Wijngaarden-Cremers et al.[70]	118 SUD	ASD: 6.7%	Higher than 1% in general population
		Roy et al.[56]	50 Asperger syndrome (20-62y)	Alcohol abuse: 10% Alcohol dependence: 8%	Higher than AUD prevalence of 6.3% in German population
		Fortuna et al.[13]	255 ASD (18-71y)	Alcohol misuse: 0.9% in 18-29y, 0.0% in 30-39y, 1.4% in >40y	Lower in all age groups than general population
		Lever et al.[39]	172 ASD without ID 172 general population controls (both groups 19-79y)	SUD in ASD: 19.6% in 19-38y, 10.6% in 39-54y, 17.8% in 55-79y, 15.9% in all ages	Lower than general population controls

ASD: Autism Spectrum Disorder, ID: Intellectual Disability, SUD: Substance Use Disorder, AUD: Alcohol Use Disorder, OR: Odds Ratio, MA: Mean Age, NS: Not Significant