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Systematic review of risk and protective factors associated with substance use and abuse in individuals with autism spectrum disorders

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Abstract

A systematic review of autism spectrum disorder and substance use and abuse was conducted based on the Preferred Reporting Items for Systematic Review and Meta-Analysis protocol guidelines (an internationally recognized standardized methodological framework for conducting systematic review). The objectives of the review were to update and extend findings reported by Arnevik and Helverschou's review of the autism spectrum disorder and substance use literature by (1) evaluating study quality via the Mixed-Methods Appraisal Tool; (2) examining autism spectrum disorder and substance abuse diagnostic measures; (3) reporting on the prevalence of co-occurring autism spectrum disorder and substance abuse; and (4) identifying risk, protective, and positive treatment factors. Twenty-six studies on substance use and abuse in autism spectrum disorder were identified through a search of MEDLINE, PsycINFO and Google Scholar. Average study quality score was 75.4%. Prevalence rates of substance abuse among samples with autism spectrum disorder ranged from 1.3% to 36%, but due to variability in sample characteristics and diagnostic measures, a general prevalence rate could not be established. Risk and protective factors, recognized in the general population, such as familial substance abuse and comorbid externalizing disorders, and factors, which may be more likely to occur in individuals with autism spectrum disorder compared to the general population, such as few social resources (i.e. sense of social belonging, breadth of social support networks, and level of social capital) and low sensation-seeking, were identified. One intervention study was identified; however, methodological limitations preclude any conclusion regarding positive treatment factors at this time. More research, using standardized measures and comparable samples, is needed to understand risk and protective factors and to determine the prevalence of co-occurring substance abuse and autism spectrum disorder.

Lay Abstract

Symptoms characteristic of autism spectrum disorder were initially believed to protect individuals with autism spectrum disorder from developing substance abuse. However, recent studies suggest that up to 36% of individuals with autism spectrum disorder may have a co-occurring issue with substance abuse. In addition, substance abuse may worsen the difficulties with daily functioning some individuals with autism spectrum disorder experience. It is important to understand occurrence rates, and risk, protective and positive treatment factors of co-occurring autism spectrum disorder and substance abuse in order to promote the best possible support for this special population. This review aimed to find and synthesize evidence regarding risk, protective and treatment factors, and determine a general prevalence rate of co-occurring autism spectrum disorder and substance abuse from all studies on substance use and abuse in individuals

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with autism spectrum disorder. The review also aimed to assess study quality and identify a diagnostic measure for substance abuse in individuals with autism spectrum disorder. Twenty-six studies on substance use and abuse in autism spectrum disorder were included in the review. The rates of substance abuse among those with autism spectrum disorder identified by included studies ranged from 1.3% to 36%, but due to large differences in study methods, a general prevalence rate could not be determined. Risk and protective factors, recognized in the general population, such as familial substance abuse and co-occurring mental health issues, and factors which may be more likely to occur in individuals with autism spectrum disorder, such as limited social resources and low sensation-seeking, were identified. No diagnostic measures specific to individuals with autism spectrum disorder and substance abuse were identified. This review identified only one exploratory study on an adapted intervention for co-occurring autism spectrum disorder and substance abuse. However, there were many methodological challenges in this study that limit the conclusions that can be drawn from the data. More research, using consistent methods, is needed to understand risk and protective factors and to determine the prevalence of substance abuse among individuals with autism spectrum disorder. The potential for co-occurring autism spectrum disorder and substance abuse should be considered by professional working in both autism spectrum disorder and substance abuse services, as finding suggests substance abuse is possible among individuals with autism spectrum disorder and may occur more frequently than previously believed. In addition, autism spectrum disorder and substance abuse service providers should be sensitive to specific risk and protective factors identified by the review that may impact substance abuse course and outcomes.

Keywords
alcohol, autism spectrum disorder, drugs, substance abuse, substance use

Substance use disorder (SUD) is a mental health condition characterized by the use of one or more substances (e.g. alcohol, tobacco, cannabis, drugs) leading to clinically significant impairment and distress (American Psychiatric Association, 2013). SUD, which includes substance addiction and substance abuse, is defined as the habitual and/or compulsive consumption of psychoactive (i.e. mind-altering) substances despite harmful social, occupational, legal and/or medical consequences (American Psychiatric Association, 2010). SUD differs from casual substance use, which is defined as the consumption of psychoactive substances; substance use in the presence of various concomitant factors (e.g. genetic vulnerability, pathology) can lead to substance abuse and ultimately SUD (World Health Organization, 2010). Although SUD and substance abuse differ in that SUD is a medical diagnosis which requires clinically significant impairment from habitual substance abuse, the terms SUD and substance abuse are frequently used synonymously in the substance use literature. For the purposes of this review, we used the term substance abuse to refer to any type of problematic substance use, including both substance abuse and SUD. In Canada, it is estimated that 21.6% of the general population meets criteria for any lifetime SUD, with alcohol, followed by cannabis being the most frequently used and abused substances (Statistics Canada, 2017). Worldwide, prevalence (i.e. proportion of a population who has a specific health condition; American Psychiatric Association, 2010) estimates of 12-month SUD range from 0% to 16% (World Health Organization, 2012). Although initially thought to be rare among individuals with autism spectrum disorders (ASDs; Woodbury-Smith et al., 2006), an emerging body of research suggests that individuals with ASD do experience substance abuse, and in fact, current prevalence rates may underestimate the actual co-occurrence of ASD and substance abuse (Adhia et al., 2020).

Although there are few empirical studies on the co-occurrence of substance abuse and ASD (van Wijngaarden-Cremers et al., 2014), a review conducted by Arnevik and Helverschou in 2016 identified 18 studies on co-occurring ASD and substance abuse. The review focused on epidemiology, patient characteristics, function of substance abuse, and existing interventions for this population. Reported rates of co-occurring ASD and substance abuse in the included studies ranged from 0.7% (Abdallah et al., 2011) to 36% (Mandell et al., 2012). The authors attempted to identify a general prevalence rate for substance abuse in adults with ASD, but this was not possible due to variability in reporting methods. For example, the majority of studies did not focus specifically on ASD and substance abuse; rather, they were more general prevalence studies of psychiatric comorbidity. Furthermore, there was wide variability in sample characteristics, such as intelligence quotient (IQ), age, sex, population (e.g. Asperger's syndrome, pervasive developmental disability), and setting (e.g. community outpatient, psychiatric forensic) among the included studies. Various methodological issues, including variability in methods for assessing substance abuse, limited reporting of participant IQ, small sample sizes and case studies, use of specialized samples, and inconsistencies in controlling for comorbid conditions limited the authors' ability to determine an overall prevalence of substance abuse in ASD. No intervention studies were identified.

In addition to the lack of empirical research on the prevalence of substance abuse among individuals with ASD,

substance abuse may also be underdiagnosed in individuals with ASD in clinical settings. Although screening for substance use issues is often a component of routine clinical assessments for many disorders, screening for substance abuse during psychiatric assessments of individuals with ASD is rarely conducted (Chang et al., 2003). This may be because of social and behavioural deficits associated with ASD, which may contribute to assumptions in clinical settings regarding the rarity of substance use in this population (Sizoo et al., 2010). For example, symptoms of repetitive and restrictive behaviours may result in strict adherence to routines and rules for some individuals with ASD, thereby reducing the likelihood of experimentation with illicit substances. Similarly, social isolation and difficulties in independent living may limit opportunities for engagement in contexts where substances are present.

In the general population, the onset of substance abuse most typically occurs during adolescence and is often accompanied by other types of pathology (Armstrong & Costello, 2002; Tarter et al., 1999). Whereas the onset of unproblematic/typical substance use is associated with environmental factors (in particular peer influence), the transition from substance use to abuse is strongly associated with genetic (Kendler et al., 2003) and psychological risk factors (Shanmugam, 2017). Recent research suggests that various substance abuse risk factors well established in the general population, such as exposure to adverse childhood experiences, may also be substance abuse risk factors for the ASD population (Butwicka et al., 2017). Furthermore, there is research that suggests that the social difficulties and maladaptive coping styles frequently seen in individuals with ASD may actually place them at greater risk for substance abuse (Kronenberg, Goossens, van Busschbach, et al., 2015), whereas other evidence suggests that characteristics associated with ASD, such as social isolation, may protect them from developing substance abuse (Rothwell, 2016). The known risk factors for substance abuse in psychiatric populations (e.g. individuals with attention-deficit hyperactivity disorder (ADHD)) are early onset of smoking (Biederman et al., 2006), disruptive behaviour in childhood (Compton et al., 2005), and parental history of substance abuse (Biederman et al., 2008). How these factors contribute to comorbid ASD and substance abuse is not yet understood.

The goal of the current review was to build on the previous work by Arnevik and Helverschou (2016) by (1) evaluating study quality via the Mixed-Methods Appraisal Tool (MMAT; Hong et al., 2018); (2) examining ASD and substance abuse diagnostic measures; (3) reporting on the prevalence of co-occurring ASD and substance abuse; and (4) identifying risk, protective, and positive treatment factors. In particular, the identification of risk and protective factors is important to guide research and clinical efforts, and information on study quality can assist in the interpretation of these findings. Given the paucity of research specific to substance abuse in ASD, and research suggesting that frequent substance use precipitates substance abuse (World Health Organization, 2004), both risk and protective factors for substance abuse and substance use more generally were examined in the current review.

Method

Design

A systematic literature review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). Prior to commencing this study, the proposed methodology was registered for PROSPERO (Record ID: CRD4201810702). PROSPERO is an international database of registration for forthcoming systematic reviews in health and social care designed to increase transparent reporting and avoid unplanned duplication (Stewart et al., 2012). Key features from the review protocol are recorded and maintained as a permanent record to enable comparison of reported review methods with what was planned in the protocol. Our search proceeded as planned with the exception that we broadened the initial search terms to include autistic trait variables (e.g. autistic traits) and substances (e.g. inhalants) not originally anticipated, in order to broaden the scope of the review given the limited research in this area. In addition, an updated search of studies published between 2018 and 2020 was conducted.

Search strategy

A search was performed to identify all studies published in English or French reporting on co-occurring ASD and substance use or abuse, either as a main focus or as a by-product of the study (e.g. prevalence studies focusing on general psychiatric comorbidities in an ASD population that included a report on substance abuse) published between 2008 and 2018. The search was limited to studies published after 2007, in order to identify only the most recent and relevant research on the topic (Gopalakrishnan & Ganeshkumar, 2013). An updated search (employing the same initial search methods) was conducted in January 2020 of studies published between 2018 and 2020. Both adult and child, qualitative, quantitative, and mixed-methods studies were included. Meta-analyses, reviews, dissertations and unpublished reports were excluded from the analysis, as were animal studies and studies published in languages other than English and French. The following databases were searched: MEDLINE, PsycINFO and Psychiatry. Searches of the grey literature (i.e. reports, government documents) were also conducted in Google Scholar. See Table 1 for a list of all included search terms. While caffeine is the most frequently consumed psychoactive substance worldwide, caffeine was not included as a substance in our review because the *Diagnostic and*

Table 1. Review search terms.

Autism-related search terms		Substance-related search terms
'ASD'		'substance abuse'
'autis*'		'substance use*'
'PDD*'	AND	'substance*'
'Asperger*'		'addict*'
'developmental disability*'		'marijuana'
'neurodevelopmental disability*'		'cannabis'
		'pot'
		'weed'
		'alcohol*'
		'drinking'
		'narcotic*'
		'pain killers'
		'prescription drug abuse'
		'inhalants'
		'tobacco'
		'Ritalin misuse'
		'opioids'

ASD: autism spectrum disorder; PDD: pervasive developmental disorder.
'OR' was inputted into database search fields to connect all alternate autism and substance-related terms searched in the review.

Statistical Manual of Mental Disorders (5th ed.; *DSM*-5; American Psychiatric Association, 2013) does not currently include a category for SUD associated with caffeine (Meredith et al., 2013).

A total of 2228 articles were identified after our initial database search, 84 from our search of the grey literature, and a further 353 after our updated search. After duplicates were removed, studies were manually screened for inclusion through title, abstract and full article review stages. At each stage, four raters independently assessed 25% of articles for inclusion and then all raters cross-blind rated a different 25%. Disagreements were discussed and resolved by consensus by all four raters. Of the 2321 studies initially screened, there were 113 discrepancies in total across all three stages of the inclusion review, yielding an inter-rater reliability of 95.13%. In total, 26 studies were deemed to have met the inclusion criteria. In cases where further analyses of study data were presented across more than one article, all articles were included (e.g. Kronenberg, Goossens, van Busschbach, et al., 2015; Kronenberg, Verkerk-Tamminga, et al., 2015). See Figure 1 for a flow diagram of the PRISMA search process.

Quality assessment

The MMAT (Hong et al., 2018) was used to assess the methodological quality of all included studies. The measure was designed to evaluate the most common types of empirical studies (qualitative, randomized controlled trials, non-randomized studies, quantitative descriptive and mixed-method research) in terms of methodological strength and risk of bias. The tool has been pilot-tested for validity and has been used worldwide in systematic mixed study reviews (Pace et al., 2012). Four reviewers independently completed the quality assessment on each included article. Studies received a total score on five criteria relevant to the study design (i.e. qualitative studies were assessed according to qualitative criteria). Studies were scored for each criterion on a pass (1) or fail (0) basis, with potential scores ranging from 0 to 5 (e.g. the criteria for quantitative descriptive studies are as follows: (1) Is the strategy relevant to address the research question? (2) Is the sample representative of the target population? (3) Are the measures appropriate? (4) Is the risk of non-response bias low? (5) Is the statistical analysis appropriate to answer the research question(s)?). See Hong et al. (2018) for a description of study criteria relevant to each study design. The quality of the design was then determined by calculating the percentage of criteria fulfilled (e.g. if a study fulfilled three of the five MMAT criteria, it received a total score of 60%). The MMAT does not provide cut-off scores for low- versus high-quality studies (i.e. the value that characterizes low- versus high-quality studies has yet to be studied). The developers instead suggest that these values depend on the context of the review and recommend that review authors define their own parameters for determining study quality in terms of MMAT scores. Due to the dearth of research specifically in the context of substance use and abuse in ASD, any study receiving a score of 40% or above on the MMAT was considered satisfactory, and methodological concerns for studies were noted as relevant to the current review results. No studies were excluded from the analysis based on MMAT score. Quality scores and MMAT missing items for each included study are presented in Table 2.

Data extraction

Four of the authors then extracted information from the articles, including (1) study (e.g. design, country where study was located) and participant (e.g. ASD measure, substance use and abuse measure, sample size, gender, age, and intellectual functioning) characteristics, (2) substances examined and substance abuse prevalence rate, and (3) findings regarding risk, protective, and positive treatment factors to substance use and abuse. Studies were also reviewed in order to identify a potential substance abuse screening tool specific to use in the ASD population. If the focus of study was not on ASD and substance use specifically (e.g. prevalence studies of psychiatric comorbidity), only data related to ASD and substance use were extracted. For example, if a study provided demographic information on both the overall sample and the participants within the sample with ASD, only the information on

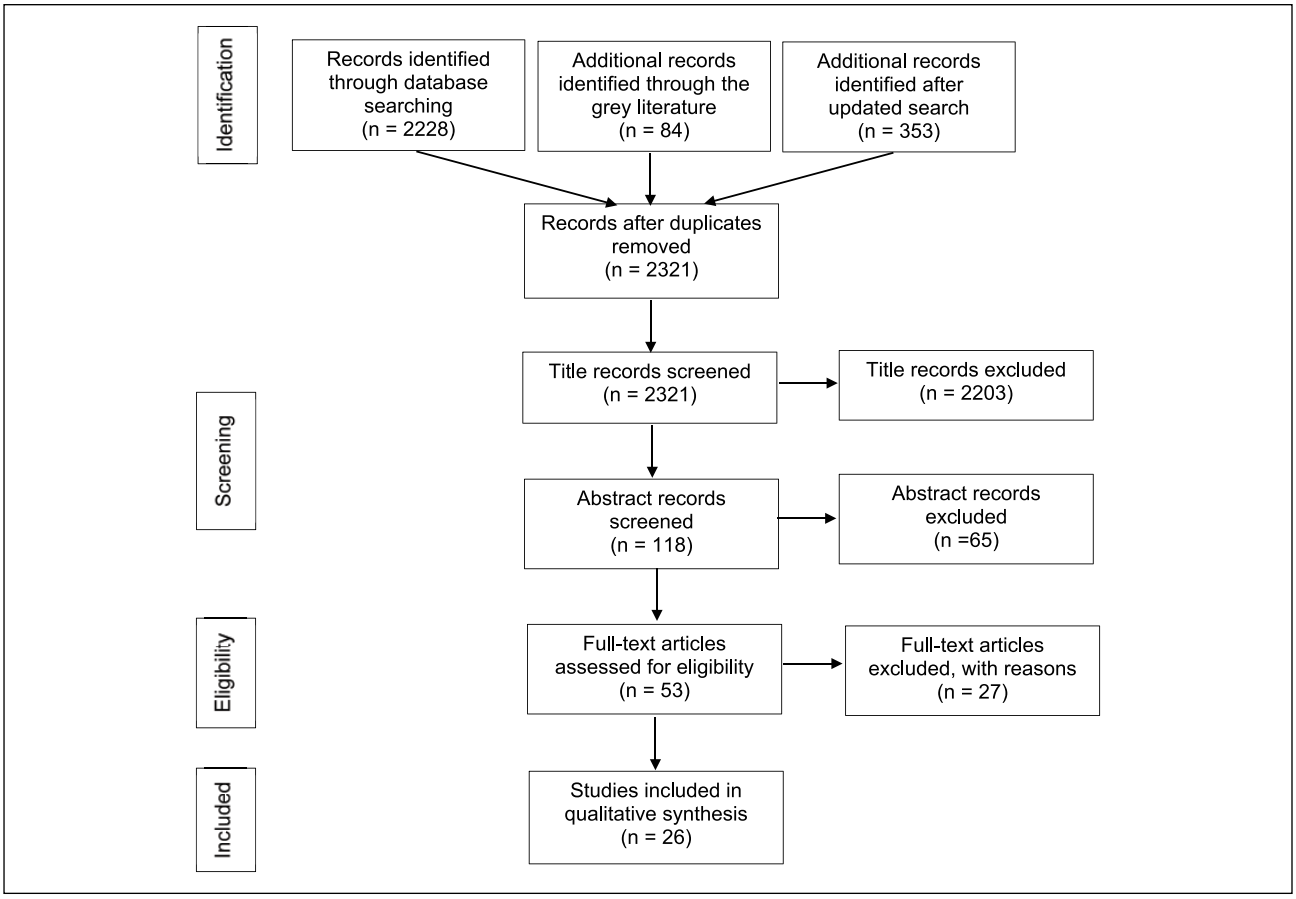

Figure 1. PRISMA flow diagram.

individuals with ASD was recorded. If studies did not directly report a prevalence rate for the occurrence of substance abuse in the ASD sample (16% of included studies), the occurrence was hand-calculated based on available information. All hand-calculated prevalence rates were verified by a second coder.

Results

A total of 26 studies were included in the analysis. Results regarding study characteristics (study focus, design, location, participant characteristics) are summarized and then further discussed based on the four identified objectives of the review.

Study characteristics

Table 2 summarizes characteristics of the 26 studies. Just over half (57.7% or 15/26) of the included studies explicitly focused on comorbid ASD and substance use and/or abuse. In terms of study design, 10 studies were prevalence, 9 were case-control, 4 were qualitative, 2 were case studies and 1 was a mixed-method treatment study. The majority (76.9% or 20/26) of studies were conducted in Europe, in particular Dutch and Scandinavian countries. Four of these studies were conducted by a single group in the Netherlands (Kronenberg, Goossens, van Busschbach, et al., 2015; Kronenberg, Slager-Visscher, et al., 2014; Kronenberg, Verkerk-Tamminga, et al., 2015; Kronenberg, Goossens, van Etten, et al., 2015). Three studies were conducted in the United States, one in Australia, and one in Israel.

Participant characteristics

Samples ranged in size from 2 to 2937 participants. Most studies (57.7% or 15/26) included adult (i.e. >18 years of age) samples; however, four included adolescents (<18 years), and four included mixed adolescent and adult samples. Three studies did not report participant age. Gender of participants was primarily male (95.6%). Samples were recruited from forensic, inpatient and outpatient psychiatric units, specialized ASD or SUD clinics, and general population settings. Most studies (61.5%) did not report on participant income, level of education, or ethnicity. For studies that included demographic information, the majority of participants were White, employed through supported-employment programmes, educated at the high-school level, and living either independently or in supported housing.

Table 2. Study characteristics.

Study	Location[a]	Study quality scores[b] and missing items	ASD/SUD focused	Population/setting	Design	Age[c]	Sex	Intellectual functioning/ FSIQ	ASD measure	SUD measure	Substances examined	Prevalence of substance use in ASD sample
Brookman-Frazee et al. (2009)	USA	80% Convenience sampling	No	Public service users (i.e. mental health, juvenile justice, child welfare, alcohol and drug, special education)	Prevalence *N* = 220 with ASD or ID	6–19	67.8% male	85% with ID	The Child Health Questionnaire (CHQ-PF28)	Involvement in alcohol/ drug services	NR	1.3% SUD
Butwicka et al. (2017)	Sweden	100%	Yes	General population	Case-control *N* = 26,986 ASD *N* = 96,557 Non-ASD relatives	NR	NR	NR	Previous diagnosis	Previous diagnosis of SUD or alcohol-related somatic disease, or conviction for substance-related crime or substance-related death	Alcohol, tobacco, drugs[d]	3.6% SUD (2.1% alcohol, 0.1% tobacco, 2.1% drugs)
Clarke et al. (2016)	UK	60% Small sample, issues with data sources	Yes	ASD or SUD outpatient services	Qualitative *N* = 8 AS	21–55	87% male	NR	Previous diagnosis	Clin. Ax. Alcohol Use Disorders Identification Test (AUDIT), Drug Abuse Screening Test (DASC)	Tobacco, drugs	NR
De Alwis et al. (2014)	Australia	60% Convenience sample, limitations with sample representativeness	Yes	General population twins	Case-control *N* = 702 individuals with ⩾ 6 AT	27–40	36.7% male	NR	>5 AT on SRS	Clin. Ax. *DSM*-IV criteria for alcohol dependence, cannabis dependence, nicotine dependence and SUD as well as the Structured Assessment for the Genetics of Alcoholism interview (SSAGA-OZ)	Alcohol, tobacco, cannabis	5.6% SUD (tobacco) 1.3% AUD 6.5% CUD
Esan et al. (2015)	UK	60% Sample representativeness	No	Forensic clinical inpatient (ID)	Cross-sectional *N* = 138 Forensic inpatient ID, 42 with ASD	ASD, *M* = 30	86% male	100% with ID	Clin. Ax. using ICD-10 criteria	Previous diagnosis	NR	11.9% SUD
Fortuna et al. (2016)	USA	80% No standardized SUD measures	No	Primary care services	Cross-sectional *N* = 255 ASD	18–71	75.3% male	50% with ID, 44% NR	Previous diagnosis	Single question (tobacco use defined as using in past 5 days, alcohol misuse defined as drinking > 5 drinks/day) on the Rochester Health Status Survey (RHSS-IV)	Alcohol, tobacco	1.9% alcohol misuse 5.2% tobacco misuse
Helverschou et al. (2015)	Norway	100%	No	Forensic archives	Cross-sectional *N* = 48 ASD	15–67	85% male	33% with ID	Previous diagnosis	Previous diagnosis	Alcohol, cannabis, drugs	15% SUD

(Continued)

Table 2. (Continued)

Study	Location[a]	Study quality scores[b] and missing items	ASD/SUD focused	Population/setting	Design	Age[c]	Sex	Intellectual functioning/ FSIQ	ASD measure	SUD measure	Substances examined	Prevalence of substance use in ASD sample
Helverschou et al. (2019)	Norway	40%, small sample limiting quantitative data analysis, sample representativeness, limited description of qualitative data analysis	Yes	Outpatient SUD services	Mixed-method treatment *N* = 4 ASD, 3 clinicians	22–44 *M* = 31.4	100% male	>70 M_{IQ} = 110.8, range = 102-125	Previous diagnosis	Alcohol Use Disorders Identification Test–Extended (AUDIT-E), Drug Abuse Screening Test–Extended (DASC-E)	Alcohol, cannabis, drugs	NA
Hofvander et al. (2009)	France & Sweden	100%	No	Psychiatric outpatient	Prevalence *N* = 122 ASD, AS, or PDD-NOS	16–60	67% male	0% with ID	Previous diagnosis	Clin. Ax. based on *DSM*-IV criteria	Alcohol, cannabis, drugs	4% SUD, 11% AUD
Kronenberg, Goossens, van Busschbach, et al. (2015)	The Netherlands	60% Non-response bias, sample representativeness	Yes	Out/inpatient SUD services	Cross-sectional *N* = 50 SUD *N* = 31 SUD + ASD *N* = 41 SUD + ADHD *N* = 1200 CTR	18–65	94% male	>80	Previous diagnosis	Previous diagnosis	Alcohol, cannabis, drugs	NA
Kronenberg, Goossens, van Etten, et al. (2015)	The Netherlands	60% Non-response bias, sample representativeness	Yes	Out/inpatient SUD services	Cross-sectional *N* = 50 SUD *N* = 31 SUD + ASD *N* = 41 SUD + ADHD	18–65	94% male	>80	Clin. Ax. using DISCO-11 criteria, ADI-R	Clin. Ax. using Mini International Neuropsychiatric Interview	Alcohol, cannabis, drugs	NA
Kronenberg et al. (2014)	The Netherlands	100%	Yes	Dual-diagnosis outpatient	Qualitative *N* = 11 SUD + ADHD *N* = 12 SUD + ASD	18–65	100% male	>80	Previous diagnosis	Previous diagnosis	Alcohol, cannabis, drugs	NA
Kronenberg, Verkerk-Tamminga, et al. (2015)	The Netherlands	100%	Yes	Clinical outpatient (dual-diagnosis services)	Qualitative *N* = 9 SUD + ADHD *N* = 12 SUD + ASD	27–54	92% male	>80	Clin. Ax. using *DSM*-IV criteria	Clin. Ax. using *DSM*-IV criteria	Alcohol, cannabis, drugs	NA

(Continued)

Table 2. (Continued)

Study	Location[a]	Study quality scores[b] and missing items	ASD/SUD focused	Population/setting	Design	Age[c]	Sex	Intellectual functioning/ FSIQ	ASD measure	SUD measure	Substances examined	Prevalence of substance use in ASD sample
Lalanne et al. (2015)	France	40%, limited description of data sampling and analysis methods, lack of data-substantiated results	Yes	Psychiatric inpatient	Case study $N = 2$ SUD + ASD	45–55	100% male	0% with ID	Clin. Ax. using *DSM*-IV criteria	Clin. Ax. using *DSM*-IV criteria	Alcohol, tobacco, caffeine	NA
Lugnegärd et al. (2011)	Sweden	80%	No	Outpatient ASD clinic	Prevalence $N = 54$ AS	$M = 27$	48% male	$M_{IQ} = 102$	Clin. Ax. using DISCO-11	Clin. Ax. using SCID-I	Alcohol, drugs	7% SUD
Lundström et al. (2011)	Sweden	80%	No	General population twin study	Cross-sectional $N = 159$ ASD	9–52	51% male	NR	>4.5 score on the Autism – Tics, ADHD, and other Comorbidities inventory (A-TAC)	Single self-report item from an online questionnaire based on *DSM*-IV criteria	Alcohol, drugs	2.5% SUD
Mandell et al. (2012)	USA	80%	No	Psychiatric inpatient	Prevalence $N = 14$ ASD	ASD, $M = 53.6$	71% male	64% with ID	Clin. Ax. based on ADI-R	Previous diagnosis	Alcohol, tobacco, drugs	36% SUD 43% tobacco use
Mangerud et al. (2014)	Norway	60% Non-response bias, sample representativeness	No	Psychiatric outpatient	Prevalence $N = 42$ ASD	13–19	46% male	NR	Clin. Ax. using ICD-10 criteria	Online self-report questionnaire assessed substance use but not SUD	Alcohol, tobacco, drugs	7.7% alcohol use, 0% drug or tobacco use
Mulligan et al. (2014)	USA	80%	Yes	General population	Case-control $N = 61$ high AT	13–17	51% male	>70	>62 on SRS	Child Behaviour Checklist (CBCL)	Alcohol, tobacco, drugs	1.6% 'High' alcohol use, 3.3% 'High' tobacco use, 3.3% 'High' drug use
Nylander et al. (2013)	Sweden	80%	No	Out/impatient psychiatric	Prevalence $N = 144$ ASD	NR	69% male	11.50% with ID	Previous diagnosis	Previous diagnosis	NR	4.8% SUD
Ramos et al. (2013)	Spain	80%	Yes	Outpatient ASD clinic	Case-control $N = 26$ AS $N = 28$ CTR	AS, $M_{age} = 15.5$	84% male	0% with ID	Clin. Ax. using *DSM*-IV criteria, ADOS & ADI-R	Interpersonal Risk Factor for Drug Use in Adolescents (FRIDA)	NR	NR
Roy et al. (2015)	Germany	80%	No	Outpatient ASD clinic	Qualitative $N = 50$ AS	20–62	68% male	NR	Self-report Questionnaire developed by authors based on *DSM*-IV criteria	Clin. Ax. using SCID-I	Alcohol, cannabis, drugs	16% AUD, 12% SUD

(Continued)

Table 2. (Continued)

Study	Location[a]	Study quality scores[b] and missing items	ASD/SUD focused	Population/setting	Design	Age[c]	Sex	Intellectual functioning/ FSIQ	ASD measure	SUD measure	Substances examined	Prevalence of substance use in ASD sample
Schapir et al. (2016)	Israel	100%	Yes	Psychiatric inpatient	Case-control *N* = 85 PDD *N* = 85 CTR	14–48	83.5% male	NR	Clin. Ax. using *DSM*-IV criteria	Lifetime use of substance (>6 months) based on a chart review of medical records	Alcohol, tobacco, cannabis	3.5% alcohol use, 20% tobacco use, 2.4% cannabis use
Sizoo et al. (2010)	The Netherlands	80%	Yes	Developmental disorder diagnostic services	Case-control *N* = 70 ASD *N* = 53 ADHD	ASD, *M* = 34.4	79% male	>80	Clin. Ax. using *DSM*-IV criteria, ADI-R	Clin. Ax. using *DSM*-IV criteria	Alcohol, cannabis, drugs	30% SUD, 14% of which AUD
Sizoo et al. (2009)	The Netherlands	80%	Yes	Developmental disorder diagnostic services	Cross-sectional *N* = 75 ASD *N* = 53 ADHD, Groups further divided into former SUD (8), current SUD (14), no SUD (53)	ASD, *M* = 34.9	80% male	>80	Clin. Ax. using *DSM*-IV criteria, ADI-R	Clin. Ax. using *DSM*-IV criteria	Alcohol, drugs	14.6% AUD, 8% CUD, 6.6% SUD
van Wijngaarden-Cremers et al. (2014)	The Netherlands	40%, sample representativeness, lack of data-substantiated results	Yes	Inpatient psychiatric	Case study *N* = 118 adult addiction psychiatry patients, 8 with ASD	NR	100% male	NR	Clin. Ax.	Measure not specified; defined as involvement in addiction psychiatric services	Alcohol, drugs	NA

ASD: autism spectrum disorder; SUD: substance use disorder; FSIQ = Full Scale Intelligence Quotient; ID: intellectual disability; NR: not reported; AS: Asperger's syndrome; AT: autistic trait; SRS: Social Responsiveness Scale; *DSM*-IV: *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM*-IV; AUD: alcohol use disorder; CUD: cannabis use disorder; Clin. Ax.: clinical assessment; *M*: mean; ICD-10: *International Statistical Classification of Diseases and Related Health Problems–10th Edition* (World Health Organization, 1992); PDD: pervasive developmental disorder; ADHD: attention-deficit hyperactivity disorder; CTR: control; NA: not applicable (i.e. studies with samples comprised entirely of individuals with ASD and comorbid ID – i.e. with 100% prevalence rate in the study); DISCO-11: Diagnostic Interview for Social and Communication Disorders (Wing et al., 2002); ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview–Revised (Lord et al., 1994); SCID-I: Structured Clinical Interview for *DSM*-IV Axis I Disorders.

NA refers to studies in which 100% of sample had SUD; therefore, prevalence rate was considered not applicable.

[a]Location based on first author's institution if study location not specified in article. [b]Study quality based on total score attained on Mixed-Methods Appraisal Tool (Hong et al., 2018).

[c]Age reported in years. [d]Drugs refer to any of the following substances: Methadone, Opiates, Heroin, Hallucinogens, Central Stimulants, Benzodiazepines, Amphetamines, Cocaine, Multi-Substance, Psychotropic Substances, Sedatives, Hypnotices, Anxiolytics.

Eight of 26 studies (30.8%) either did not assess or did not report participant IQ. Participants in three of these eight (Clarke et al., 2016; Ramos et al., 2013; Roy et al., 2015) studies were exclusively diagnosed with Asperger's syndrome, a condition that was distinguished from autism (in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM*-IV-TR)) by average or better language skills and intellectual ability (Hofvander et al., 2009; Ozonoff et al., 2000). Thus, we suspect that these three studies included participants with average or above IQ. Six studies (23.0%) included samples of individuals with ASD and comorbid intellectual disability, and the remaining 12 (46.2%) included samples with average IQ (⩾70). In terms of method of IQ assessment, just over one quarter of studies (26.9% or 7/26) reported using standardized measures of IQ (e.g. *Wechsler Adult Intelligence Scale–Third Edition* (WAIS-III)).

Objective 1: study quality assessment

Study quality was generally satisfactory; across the 26 articles included in our review, the average score was 75.4% on the five MMAT criteria. Scores ranged from 40% to 100%. Six of 26 studies passed all five MMAT criteria, receiving an overall methodological rigour score of 100%. The most consistent rating of included studies on the MMAT was 80%; 11 studies received this score. Five studies scored 60%, and three studies received our minimum MMAT score requirement for inclusion of 40%. Specific methodological concerns for each study that received a score of 80% or below on the MMAT are included in Table 2. Methodological limitations have also been noted for results regarding risk, protective and positive treatment factors when relevant to the strength of the evidence.

Objective 2: ASD and substance abuse assessment methods

ASD assessments. There was variability across studies in the means by which ASD was defined and assessed (see Table 2). Twelve studies confirmed ASD diagnosis via clinical assessments conducted by the research team using standardized measures (e.g. Autism Diagnostic Interview Schedule), while nine studies used proof of previous diagnosis. Three studies defined ASD in terms of 'high autistic traits' based on standardized self-report measures, such as the Social Responsiveness Scale (two studies; SRS) or the Autism – Tics, ADHD, and other Comorbidities inventory (one study; A-TAC). One study used an author-developed self-report measure based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM*-IV) criteria for ASD. Finally, one study of child/adolescent participants (6–19 years) used parent-reported ASD measures (e.g. the Child Health Questionnaire). Findings based on ASD samples diagnosed via standardized clinical assessments (either conducted by the researchers themselves or obtained from previous assessment reports via chart review) were not considered comparable to studies with self-reported ASD or autistic traits for the purposes of this review. As such, risk and protective factor findings from studies which examined substance use and autistic traits have been placed in a separate section. Furthermore, the implications regarding risk and protective factors identified by studies which included a self/parent report diagnostic measure should be interpreted with caution, and have been noted in the relevant sections.

Substance use assessments and screening tools. There was also variability across studies on substance use measures employed (see Table 2). Eleven studies diagnosed substance abuse based on a standardized clinical assessment conducted by the research team (e.g. Structured Clinical Interview for *DSM*-IV Axis I, SCID-I; Alcohol Use Disorders Identification Test, AUDIT). Two used single items on self-report questionnaires. Eight categorized substance abuse as current or previous diagnosis of SUD. Two defined substance abuse in terms of involvement in drug/alcohol services and two investigated substance use via self-report questionnaires but not substance abuse specifically (e.g. Interpersonal Risk Factor for Drug Use in Adolescents, FRIDA). One study examining the relations between autistic traits and substance use in an adolescent sample (13–17 years) used substance-related items on a parent-report questionnaire of general child behaviour problems (Child Behaviour Checklist (CBCL)). Assessment measures designed specifically to screen for substance abuse in individuals with ASD were not found. Similar to review findings from studies which included self-report/unstandardized measures of ASD, findings from studies that included self-report or non-standardized measures of substance abuse were considered to be of a lower strength of evidence than those extracted from studies that included standardized clinical methods of assessing substance abuse and have been noted in the relevant results section. Because substance use and abuse may be over or underrepresented (in terms of both frequency and severity) in samples wherein non-clinical measures were employed, findings regarding risk and protective factors in these studies should be interpreted with caution.

Objective 3: prevalence of substance abuse in ASD samples

In prevalence studies that focused on clinical levels of substance abuse (as opposed to substance use more generally), reported prevalence rates of substance abuse ranged from 1.3% to 36% in the ASD sample. Due to differences across studies in terms of sample and study methods, the identification of a prevalence rate was not possible. For studies that reported specifically on types of substances used, tobacco, followed by alcohol and then cannabis, was

reported most often as the substance of choice in individuals with ASD. Few studies reported on the rates of substance abuse associated with these substances (25%). Rates of alcohol use disorder (AUD) ranged from 1.3% (De Alwis et al., 2014) to 16% (Roy et al., 2015). Two studies also reported on cannabis use disorder (CUD) reporting 6.5% (De Alwis et al., 2014) and 8% (Sizoo et al., 2009) rates of occurrence among their ASD sample.

Objective 4a: risk factors

Table 3 summarizes identified risk and protective factors. Fifteen studies investigated risk factors for SUD in individuals with ASD. Of these 15 studies, 8 quantitative and 4 qualitative studies identified several risk factors for SUD in ASD, including risk factors related to individual psychiatric characteristics, individual cognitive characteristics and environmental factors. Three studies examined factors that were found to be statistically non-significant (comorbid externalizing disorder; Brookman-Frazee et al., 2009; Lugnegärd et al., 2011; perceived social deficits and psychological distress; Helverschou et al., 2019). It is also important to qualify that no longitudinal studies were identified, and the 15 studies were cross-sectional or case-control designs. Therefore, the results regarding risk and protective factors are correlational and should be interpreted cautiously.

Individual psychiatric characteristics. Five individual psychiatric risk factors were identified through this review.

ASD diagnosis. Two studies with large samples found ASD to be a significant risk factor for substance abuse. First, in a cross-sectional study of 27,468 individuals, the risk of substance abuse was six times greater in participants with an ASD diagnosis than those in the no autistic traits comparison group (Lundström et al., 2011). However, a single self-report item was used to assess substance use (i.e. 'Do you have or have you ever had problems with alcohol or drugs? Y/N'). Similarly, in a high-quality (score of 100% on the MMAT) population-based cohort study of 26,986 individuals with ASD, and 96,557 non-ASD relatives controls, an ASD diagnosis without comorbid ADHD or intellectual disability doubled the risk of substance use–related problems, defined as substance abuse, somatic disease related to alcohol misuse, substance-related crime, and death (i.e. deaths attributed directly or indirectly to the use of psychoactive substances such as death by intoxicated driving; Butwicka et al., 2017).

High autistic traits. Three studies found autistic traits were significantly associated with elevated risk of substance use and abuse (De Alwis et al., 2014; Lundström et al., 2011; Mulligan et al., 2014). Lundström et al. (2011) found that the risk of substance abuse (defined as endorsement of a single dichotomous item: 'Do you have or have you ever had problems with alcohol or drugs?') in individuals stratified according to self-reported level of autistics traits (12 *DSM*-IV-based items on autistic disorder) decreased as the level of autistic traits decreased (i.e. participants with the highest level of autistic traits were most likely to report substance abuse). In a cross-sectional study of 2937 adolescents (13–17 years old), Mulligan et al. (2014) found that individuals with elevated autistic traits (defined as raw SRS score of 62 (in the 95th percentile of the sample) without ADHD) were at significantly increased risk for 'high drug use' (defined as endorsement of three substance-related items on the CBCL). In a cross-sectional study of 3080 adult twins from the general population, high (i.e. six or more) autistic trait scores were associated with elevated levels of regular smoking and cannabis use, and alcohol, nicotine, and CUDs (De Alwis et al., 2014). The study received a rating of 60% on the MMAT due to issues with sample representativeness, as all participants were twins. Factors specific to twins may limit the generalizability of these findings to other individuals with ASD. While results from these three studies suggest that a high number autistic traits may increase the risk of substance use, due to limitations of substance abuse measures, conclusions regarding the association between substance *abuse* and autistic traits cannot be drawn. Furthermore, results regarding the association between substance use and self-/parent-reported autistic traits cannot be considered generalizable to individuals with a diagnosis of ASD based on standardized clinical assessments.

Comorbid externalizing disorders. In a random sample of 1603 youths from the public service system (i.e. mental health, educational services for youth with serious emotional disturbance, child welfare, juvenile justice, and alcohol and drug services) divided into a group with ASD and intellectual disability ($n = 220$) and a comparison group without ASD or intellectual disability ($n = 1383$), youths with ASD or intellectual disability were less likely to be involved in alcohol/drug treatment programmes (1.3% vs 3.8%) although this difference was not statistically significant. However, of those youths with ASD/intellectual disability involved in the drug/alcohol treatment programmes, 80.9% had comorbid ADHD and/or oppositional defiant disorder and 30.6% had conduct disorder. The results suggest that youth with ASD or intellectual disability may be less likely to be in a drug/alcohol treatment programme except when a comorbid externalizing disorder is present (Brookman-Frazee et al., 2009).

Attention-deficit hyperactivity disorder. In a population-based cohort study of 26,986 individuals diagnosed with ASD between 1973 and 2009, and their 96,557 non-ASD relatives, Butwicka et al. (2017) found that the risk of substance use–related problems was the highest among

Table 3. Summary of factors examined in studies as potential risk and protective mechanisms of substance abuse in individuals with ASD.

	Brookman-Frazee et al. (2009)	Butwicka et al. (2017)	Clarke et al. (2016)	De Alwis et al. (2014)	Esan et al. (2015)	Fortuna et al. (2016)	Helverschou et al. (2015)	Helverschou et al. (2019)	Hofvander et al. (2009)	Kronenberg, Goossens, van Busschbach, et al. (2015)	Kronenberg, Goossens, van Etten, et al. (2015)	Kronenberg et al. (2014)	Kronenberg, Verkerk-Tamminga, et al. (2015)	Lalanne et al. (2015)	Lugnegärd et al. (2011)	Lundström et al. (2011)	Mandell et al. (2012)	Mangerud et al. (2014)	Mulligan et al. (2014)	Ramos et al. (2013)	Schapir et al. (2016)	Sizoo et al. (2010)	Sizoo et al. (2009)
Risk factors																							
Individual factors																							
ASD diagnosis		✓														✓							
High autistic traits				✓												✓			✓				
Comorbid ADHD	X	✓													X								
PDD-NOS diagnosis									✓														
Comorbid ODD	X																						
Comorbid mood disorder														a									
Comorbid CD	X																						
Comorbid anxiety														a									
Perceived social deficits			a					X					a	a									
Psychological distress			a					X				a	a										
High social motivation																							✓
Executive dysfunction												a		a									
Maladaptive coping style										✓													
Environmental factors																							
Familial history of SUD[1]		✓														✓						✓	
Early smoking onset																						✓	
Adverse family events																						✓	
Few social resources			a																				
Lack of structure												a	a	a									
Late ASD diagnosis													a										
Protective factors																							
Individual factors																							
Diagnosis of ASD					✓	✓	X										✓	X		✓			
Comorbid ID		X																					
Low sensation-seeking																				✓			
Environmental factors																							
Friends																				✓			
Access to drugs																				✓			

ASD: autism spectrum disorder; ADHD: attention-deficit hyperactivity disorder; PDD-NOS: pervasive developmental disorder–not otherwise specified; ODD: oppositional defiant disorder; CD: conduct disorder; SUD: substance use disorder; ID: intellectual disability.
✓ = indicates a significant finding with respect to at least one variable ($p < 0.05$); X = indicates the variable was investigated but no significant finding identified; a = denotes findings from qualitative analyses.
[1]Among first-degree relatives.

individuals with ASD and comorbid ADHD. In a study of psychiatric comorbidity of 26 men and 28 women with a clinical diagnosis of Asperger's syndrome, Lugnegärd et al. (2011) found substance abuse disorders to be uncommon (11%). Even though the rate of substance abuse was relatively small in the group as a whole, most of the variance for substance abuse was accounted for by individuals (8 females and 8 males) with Asperger's syndrome who also had a diagnosis of ADHD.

Mood and/or anxiety problems. Two studies found the presence of comorbid mood and anxiety disorders may also increase the risk of substance use in people with ASD. In a qualitative case study of two adults with ASD without intellectual disability and comorbid AUD, both participants had diagnosed co-occurring mood disorders (i.e. bipolar disorder and major depressive disorder) and anxiety disorders (i.e. generalized anxiety disorder) (Lalanne et al., 2015). Alcohol was reported to be a means of alleviating low mood and high levels of anxiety for these two participants. These results should be interpreted cautiously, as this study received the lowest score (40%) among the included studies in our assessment of methodological quality and risk of bias. Specifically, there were issues with lack of reporting of data sampling methods, insufficient description of within-case analysis, and limited reporting of data-substantiated results. It is unclear from these findings whether mood and anxiety problems are a risk for, or consequence of, substance abuse. However, the findings regarding the relation between mood and anxiety problems and substance abuse in individuals with ASD were consistent with those of another study that was rated as methodologically strong (Kronenberg et al., 2014). In a qualitative study of adults with ASD ($n=12$) or ADHD ($n=11$) seeking treatment for SUD, Kronenberg et al. (2014) found that substances served to alleviate feelings of anxiety, and in particular, social anxiety, for participants. This study received a score of 100% on the MMAT by two independent raters, suggesting strong methods and limited risk of bias.

Individual cognitive characteristics. Five individual cognitive characteristics were identified as risk factors through this literature review, including perceived social deficits, high social motivation, psychological distress, weak executive functioning and maladaptive coping styles.

Perceived social deficits. Three qualitative studies and one mixed-methods treatment study found that the perception of social difficulties was associated with substance abuse for individuals with ASD and average intelligence. Substances were used by adults with ASD to cope with social events (Lalanne et al., 2015) and to suppress feelings of insecurity in social situations (Kronenberg et al., 2014). Participants reported that substances increased confidence and ease of communication, reducing anxiety associated with socializing (Clarke et al., 2016; Helverschou et al., 2019), although the statistical significance of these results could not be determined due to small sample sizes.

High social motivation. In one study, clients with ASD and a current or past history of drug or alcohol dependence reported more social traits (i.e. high reward dependence defined as high desire for social interaction and high social interest) than clients with ASD and no history of SUD (Sizoo et al., 2009).

Psychological distress. Three qualitative studies and one mixed-method treatment study with samples ranging from 4 to 12 ASD participants found psychological distress to be associated with substance use and abuse. In a study of the everyday life consequences of 23 adults with substance abuse and either ASD ($n=12$) or ADHD ($n=11$), participant interviews revealed that a high level of psychological distress (associated with difficulties with coping with negative thoughts and emotions) was the primary precipitator to substance use for participants (Kronenberg et al., 2014). Similarly, in a qualitative study on the personal recovery process of 21 individuals with substance abuse and co-occurring ADHD ($n=9$) or ASD ($n=12$), each identified high levels of psychological distress (e.g. 'not being able to live a normal life') and difficulty coping with overwhelming thoughts and emotions, as associated with substance use, abuse, and SUD (Kronenberg, Verkerk-Tamminga, et al., 2015). In a small exploratory treatment study of men ($N=4$) with co-occurring ASD and substance abuse, and normal intelligence ($M_{IQ}=110.8$), three of the four participants identified reducing psychological distress and improved psychological well-being (e.g. 'to get peace, forget problems, and conflicts') as the primary reason for beginning substance use on a preintervention assessment of positive and negative aspects of substance intoxication via the Drug Use Disorder Identification Test–Extended (DUDIT-E; Hildebrand, 2015) and Alcohol Use Disorders Identification Test–Extended (AUDIT-E; Berner et al., 2007). In another, study (60% MMAT score), substance use began as a way to redirect and distract from distressing negative cognitions and self-appraisal, or to dampen the aversive emotional response and negative ruminations in eight participants with Asperger's syndrome (Clarke et al., 2016).

Weak executive functioning. Two qualitative studies reported weak executive functioning to be associated with ASD (without intellectual disability) and substance abuse. In a case study of two adults with ASD and substance abuse, weak executive functioning abilities, as indexed by low scores on standardized tests of attention, set-shifting, cognitive flexibility, and working memory (e.g. WAIS-III, Trail making Test, Six Elements Test), were associated with substance use. Both participants reported using

psychostimulants such as tobacco and caffeine to improve neurocognitive abilities (Lalanne et al., 2015). Accumulated executive functioning deficits (defined as intention formulation, initiation and execution) contributed to difficulties with self-management in 12 individuals with ASD, and later substance abuse as a form of coping (Kronenberg et al., 2014).

Maladaptive coping style. One cross-sectional study on the coping styles of 122 adult psychiatric patients with substance abuse ($n=50$), substance abuse and ADHD ($n=41$), or substance abuse and ASD ($n=31$), and a 1200 adult railway worker comparison group found elevated scores of maladaptive coping on the Ultrecht Coping List across all three patient groups, namely, Palliative Reaction (attempting to feel better through distraction, relaxing, or smoking/drinking), Avoidance, and Passive Reaction (rumination, retreating, inability to act) subscales (Kronenberg, Goossens, van Busschbach, et al., 2015). However, the ASD with substance abuse group showed significantly more disengaging coping behaviour, suggesting a tendency to ruminate about problems, feel incapacitated to do anything about the problem, and limited use of adaptive strategies such as expressing emotions or self-encouragement. It is important to note that this study was rated as having 60% study quality due to issues with the comparison group (i.e. matched only on age and gender demographics) and limited reporting of data analytic methods.

Environmental risk factors. Finally, six environmental risk factors were identified as associated with substance use or abuse in individuals with ASD.

Late ASD diagnosis. In a qualitative study, participants with ASD ($N=12$) reported feeling they would have 'lost less' and their substance use may not have developed into an substance abuse if they had been diagnosed earlier in life (Kronenberg, Verkerk-Tamminga, et al., 2015). They felt that an earlier ASD diagnosis may have increased support from family and friends.

Few social resources. The same qualitative study found limited social support was linked to initiating and maintaining substance abuse for individuals with ASD (Kronenberg, Verkerk-Tamminga, et al., 2015). Although study quality was rated as 60%, the findings were consistent with those found in Clarke and colleagues' (2016) qualitative case study, identifying few social resources with which to cope with life's stressors, as a precursor to substance use.

Lack of structure. Three qualitative studies identified lack of structure in leisure and activities of daily living as a precipitant to substance use. All participants reported that trouble with organizing and structuring lives led to participation in few daytime activities and using substances as a means to fill time, and to alleviate boredom and melancholia (Kronenberg et al., 2014; Kronenberg, Verkerk-Tamminga, et al., 2015; Lalanne et al., 2015).

Familial history of SUD. Three studies found associations between familial history of substance abuse and substance abuse in individuals with ASD. In a study on the association between autistic traits and mental health problems in two population twin cohorts of children and adults (consisting of 11,222 children and 18,349 adults), 86% of the correlation between autistic traits and substance abuse was accounted for by common genetic effects (Lundström et al., 2011). Another study of 26,986 individuals diagnosed with ASD and their 96,557 non-ASD relatives found ASD doubled the risk of substance use–related problems. Full-siblings, half-siblings and parents of those with ASD were also found to have elevated risk, suggesting shared familial (genetic and/or environmental) vulnerability (Butwicka et al., 2017). A study of risk factors and functional disability in 123 treatment-seeking adults with ASD ($n=70$) or ADHD ($n=53$) found that having at least one parent with problematic alcohol or drug use was a significant risk factor for developing substance abuse for both groups (Sizoo et al., 2010).

Early smoking onset. Regular smoking (at least one cigarette once a day for one year) early in life was a significant predictor of SUD for both individuals with ASD and those with ADHD (Sizoo et al., 2010), although 'early age' was not defined.

Family history of adversity. Sizoo and colleagues (2010) also found that more adverse childhood experiences within the context of the family environment (defined as the presence of sexual, physical, or emotional abuse, a history of severe and enduring problems with family members, and/or the absence of close, long, and personal relationships with family members) was a significant risk factor (odds ratio (OR) = 2.67) for developing substance abuse for individuals with ASD and ADHD.

Objective 4b: protective factors

Four studies independently identified four statistically significant factors that may decrease the risk of substance use or abuse for individuals with ASD. These were related to one individual personality (low sensation-seeking), one individual psychiatric (diagnosis of comorbid ASD and intellectual disability), and one environmental (limited access to drugs) protective factor. One study also found that a diagnosis of ASD may protect against substance abuse in adolescents recruited from a general clinical sample although the statistical significance of these results was not assessed.

Low sensation-seeking. In a study of 26 adolescents diagnosed with Asperger's syndrome and 28 typically developing adolescents, Ramos and colleagues (2013) examined interpersonal and personality risk factors for drug use. Adolescents with Asperger's syndrome who had lower sensation-seeking were at lower risk for drug use.

Diagnoses of comorbid ASD and intellectual disability. Four studies found diagnoses of co-occurring ASD and intellectual disability may protect against the use of substances. In a large population-based sample, individuals with ASD had a substantially increased risk of substance-related problems, but comorbid ASD and intellectual disability was not associated with an increased risk of any substance-related problem (Butwicka et al., 2017).

A cross-sectional study of health conditions in adults with ASD aged 18 to 71 years ($N=255$) found that both young (18–29 years of age) and older adults (40 years and older) with ASD (91% with intellectual disability) had significantly lower rates of tobacco use (5.2% vs 31.9%, and 2.8% vs 24.5%, respectively) and alcohol abuse (0.9% vs 11.9%, and 1.4% vs 18.2%) compared to the general population (Fortuna et al., 2016). It should be noted that the results regarding both tobacco use and alcohol abuse were based on responses to a single item on the Rochester Health Status Survey (tobacco use defined as using in past 5 days, alcohol abuse defined as drinking >5 drinks/day). Similarly, in a study of 138 adults treated in a forensic intellectual disability hospital, harmful use or dependence on drugs was significantly ($p=0.004$) lower in the 42 patients with ASD compared to those without an ASD diagnosis (11.9% vs 35.4%; Esan et al., 2015). All participants had a comorbid diagnosis of intellectual disability (based on *International Statistical Classification of Diseases and Related Health Problems–10th Edition* (ICD-10) criteria). Hence, these results may not generalize to individuals with ASD without comorbid ID. Another difficulty with interpreting the findings in this study is that no information was provided on the psychometric properties of the ASD and substance abuse measures used.

In a sample of 141 adults in a state psychiatric hospital in the United States, those who had ASD (10%; most also had intellectual disability) were significantly less likely to have a history of substance abuse (35.7% vs 78.7%) (Mandell et al., 2012).

ASD diagnosis. In a study of 566 adolescent (13–19 years) psychiatric patients compared to 8173 adolescents from the general population, the clinical sample was found to have a higher prevalence of smoking and over four times OR of having tried illicit drugs. However, the ASD group ($n=39$) reported the lowest frequencies within the clinical sample. None of the adolescents with ASD reported having tried illicit substances or being current smokers, and only 7.7% were current alcohol users (compared to 55.4% of the general population control). The study quality was 60% due to issues with non-response bias and sample representativeness since the IQ of the ASD sample was not reported (Mangerud et al., 2014). Furthermore, the statistical significance of the difference in rates of substance use between the ASD and general psychiatric sample was not assessed.

Limited access to drugs. Ramos et al. (2013) found that 26 adolescents with Asperger's syndrome (IQ > 70) were at significantly decreased risk for drug use compared to typically developing teenaged comparisons ($n=28$) derived from friend and drug access–related factors. Findings indicated that the Asperger's syndrome group's friends tended to be non-users and have negative attitudes towards drugs. In addition, adolescents with Asperger's syndrome were less likely to be exposed to contexts that facilitate opportunities for drug access and use.

Objective 4c: treatment outcome factors

Our review identified only one study specifically assessing substance abuse interventions for individuals with ASD (Helverschou et al., 2019). A mixed-methods exploratory study of four adult males previously diagnosed with Asperger's syndrome and three therapists who were trained to individually administer cognitive behavioural therapy (CBT) adapted based on clients' ASD specific needs found increased overall functioning on the Global Assessment of Functioning and a reduction in substance-related symptoms on the AUDIT-E or DUDT-E at post-intervention in three of the four participants. Thirty to forty sessions of CBT in an outpatient substance abuse clinic were administered weekly, adapted individually in order to address patient communication and comprehension deficits. Patient acceptability of the treatment was rated as high on the Patient Satisfaction Survey. The study was rated to be of the lowest potential quality for inclusion in our review on the MMAT (40%), due to the small and unrepresentative sample as well as the high attrition and no information on the qualitative analysis of the interview data. Thus, findings should be interpreted with caution.

Discussion

In the current review, we identified 26 studies, with 15 specifically focused on individuals with ASD (or autistic traits) and substance use or abuse. We extended previous findings (Arnevik & Helverschou, 2016) by evaluating the quality and risk of bias of studies conducted on ASD and substance abuse and by identifying risk and protective factors associated with substance use and abuse in individuals with ASD.

Study quality, characteristics and ASD/ substance use diagnostic measures

Although this area of study is still in its infancy, the quality of studies was generally satisfactory, ranging from 40% to

100%. Over 40% of included studies (11 of 26, or 42.3%) were rated 80% or above on the quality measure, suggesting methodological rigour and attention to limiting the bias in research on substance use and abuse among individuals with ASD. The study design (i.e. case study, qualitative, prevalence, case-control, mixed-methods), topic of focus (e.g. prevalence of general psychiatric comorbidity in an ASD sample vs examination of the function of substance use for individuals with Asperger's syndrome), and types of samples (e.g. offenders or patients in mental hospitals) varied considerably. Sample sizes, participant age, intellectual functioning and sex distribution of participants also varied across studies. Few studies reported formal diagnostic criteria for substance abuse based on standardized clinical measures (as many studies did not specifically focus on the topic), and definitions of substance abuse ranged from 'involvement in drug and alcohol treatment programs' to a single item on a self-report questionnaire. Our review did not identify any substance abuse assessment or screening measures specifically designed for the ASD population. There were differences across studies on how ASD was operationalized; a few used self- or parent-report questionnaires of autistic traits, others, standardized clinical measures, and still others used previous diagnosis from clinical records. Differences with regard to sample and study characteristics did not allow aggregation of data across studies to establish a prevalence rate of co-occurring substance abuse and ASD.

Risk, protective and positive treatment factors for substance use and abuse in ASD

We were able to identify risk and protective factors associated with the initiation of substance use and abuse in individuals with ASD. With regard to risk factors, individuals with ASD were susceptible to common risks known to exist in the general population such as familial history (i.e. heritability and environmental factors) of substance abuse, adverse family events, early tobacco use, psychological distress, and co-occurring internalizing (i.e. anxiety) and externalizing disorders (i.e. ADHD, oppositional defiance disorders) (Kendler et al., 2003). With regard to protective factors, individuals with ASD may have lower risk of substance use and substance abuse if they have low sensation-seeking traits, co-occurring intellectual disability, and limited access to drugs.

A number of risk factors which may be more likely to occur in, or unique to, individuals with ASD were also identified, including low social support, disengaging coping behaviours, late ASD diagnosis, and weak executive functioning. For example, limited social support coupled with social deficits may increase the risk of substance abuse for individuals with ASD. Furthermore, social isolation and difficulties with structuring daily activities (compounded by executive functioning deficits) may lead to difficulties with self-management and higher risk for substance use. A vicious cycle may ensue wherein substance use contributes to further lack of structure creating more difficulties with organization.

A diagnoses of ASD was identified as a protective factor to substance use and abuse when it co-occurred with intellectual disability (Butwicka et al., 2017; Esan et al., 2015; Mandell et al., 2012; Mangerud et al., 2014) but a risk factor when the individual had average or above-average intelligence (Butwicka et al., 2017; Lundström et al., 2011). Social impairments associated with ASD may limit exposure to social situations where substances are easily accessible. However, it is also possible that socially motivated and more able individuals do find themselves in social circles where substance use is more common and become users. For example, there is preliminary evidence that in a subgroup of individuals with ASD and average intellectual functioning, who report high levels of social attachment, dependence on approval of others (e.g. the desire to 'fit in'), and social interest, the risk of substance abuse may be elevated compared to other individuals with ASD (Sizoo et al., 2009). Further study of the relations between social competence and the risk for substance abuse in ASD is needed to substantiate these findings.

Our findings regarding a potential subgroup of socially motivated individuals with ASD without intellectual disability is consistent with the expectancy hypothesis of substance use (Brown et al., 1987). This theory posits that the fulfilment of specific expectations that an individual holds regarding a substance leads to its increased and continued use. When applying the theory to the ASD population, it is plausible to speculate that individuals with social difficulties may be motivated by the expectation that substances will facilitate positive social interactions and assertiveness. For example, positive social alcohol expectancies (i.e. beliefs regarding the desirable social effects of drinking) were found to mediate the relationship between social anxiety and problematic drinking in college students (Ham, 2009). Young people and adults with ASD and average intelligence often experience loneliness and a desire for social interaction, but struggle to achieve it (Mazurek, 2014; Shulman & Agam, 2003), and substance use may be viewed as aiding social engagement.

The findings also suggest that substances may serve a specific purpose for those with ASD and substance abuse. Consistent with the self-medication hypothesis, which proposes that a substance is used for its psychoactive properties that subjectively diminish psychological distress and increase cognitive control (Khantzian, 1997), our findings suggest that both psychological distress and executive functioning deficits increase the risk of substance use for some individuals with ASD. Individuals with ASD reported using substances to alleviate psychological distress and negative cognitions, as well as difficulties with initiation. These findings are important because although

not a core diagnostic feature of ASD, both executive functioning difficulties and psychological distress may occur at higher rates in individuals with ASD (Howlin & Magiati, 2017), thereby increasing the risk of SUD in individuals with ASD compared to the general population.

Currently, clinicians working with patients with ASD and substance abuse must rely on clinical expertise (which may be limited to experience in either ASD or addictions) and general guidelines for working with these patients. However, individuals with ASD and substance abuse would benefit from the establishment of treatment guidelines and collaborative service models that take into account the special needs of this population. This review identified only one exploratory study on an adapted CBT intervention for co-occurring ASD and substance abuse. However, there were many methodological challenges in this study that limit the conclusions that can be drawn from the data.

Limitations

The MMAT assesses study quality in terms of the adequacy of a given study's methods in addressing the study's specific objectives. Because our review did not focus specifically on ASD and substance abuse, but rather studies pertaining to substance use and ASD more generally, the MMAT may not have adequately captured the methodological concerns highlighted by our extraction of study design information. For example, a study on substance use in individuals with ASD may have sufficiently fulfilled study objectives by assessing substance use with a single item in a self-report questionnaire, but may represent a methodological concern for the purposes of our review. Finally, because data from the included studies were cross-sectional in nature, it is not possible to establish the causal direction of risk and protective factors identified in our review.

Conclusions and future directions

The co-occurrence of ASD and substance abuse may be more common than previously recognized, particularly in individuals who are more cognitively able, socially motivated, and those who have comorbid externalizing disorders, and individual (e.g. maladaptive coping styles, executive functioning deficits) and environmental risk factors (e.g. familial history of substance abuse, low social support) for substance abuse. Substance abuse is associated with poorer overall quality of life and functional outcomes in people with ASD (Sizoo et al., 2010). Despite the negative consequences associated with this dual diagnosis, there is little research and clinical expertise on this topic.

Future research must employ standardized measures of both substance abuse and ASD, to establish an accurate prevalence rate of substance abuse in ASD and to better understand how the diagnosis of ASD contributes to risk for or protects against substance use and abuse. Investigating potential risk and protective factors not identified in our review but that may be relevant based on what we know about ASD, such as motivational (e.g. atypical response to reward contingencies), social coping (e.g. camouflaging/masking), and sensory issues (e.g. sensitivities), would be informative. Further exploration of the social expectancies hypothesis is warranted as there is preliminary evidence that a subgroup of individuals with ASD and average intelligence who report higher social motivation or interest may be at elevated risk of substance use.

Research and clinical efforts would be limited without the development or adaptation of substance abuse measures for use in the ASD population. This would facilitate the adaption of evidence-based substance abuse interventions for people with ASD. Prevention and intervention guidelines could then be developed and disseminated widely to clinicians working in addictions and ASD services.

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