CHAPTER 3

PREVALENCE OF ATTENTION-DEFICIT HYPERACTIVITY DISORDER IN SUBSTANCE USE DISORDER PATIENTS: A META-ANALYSIS AND META-REGRESSION ANALYSIS

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Drug and Alcohol Dependence. 2012;122(1-2):11-19.

ABSTRACT

Context: Substance use disorders (SUD) are a major public health problem. Attention deficit hyperactivity disorder (ADHD) is a comorbid condition associated with both onset and prognosis of SUD. Prevalence estimates of ADHD in SUD vary significantly.

Objective: To obtain a best estimate of the prevalence of ADHD in SUD populations.

Data sources: A literature search was conducted using MEDLINE, PsycINFO and EMBASE. Search terms were ADHD, substance-related disorders, addiction, drug abuse, drug dependence, alcohol abuse, alcoholism, comorbidity, and prevalence. Results were limited to the English language.

Study Selection: After assessing the quality of the retrieved studies, 29 studies were selected. Studies in which nicotine was the primary drug of abuse were not included.

Data Extraction: All relevant data were extracted and analysed in a meta-analysis. A series of meta-regression analyses was performed to evaluate the effect of age, primary substance of abuse, setting and assessment procedure on the prevalence of ADHD in a variety of SUD populations.

Data synthesis: Overall, 23.1% (CI: 19.4% - 27.2%) of all SUD subjects met DSM-criteria for comorbid ADHD. Cocaine dependence was associated with lower ADHD prevalence than alcohol dependence, opioid dependence and other addictions. Studies using the DICA or the SADS-L for the diagnosis of ADHD showed significantly higher comorbidity rates than studies using the KSADS, DISC, DIS or other assessment instruments.

Conclusions: ADHD is present in almost one out of every four patients with SUD. The prevalence estimate is dependent on substance of abuse and assessment instrument.

INTRODUCTION

Substance use disorders (SUD) are a major public health problem. The Epidemiologic Catchment Area Study reports a lifetime prevalence for alcohol use disorders of 13.5% and for other drug use disorders of 6.1%,[1] and in the Netherlands Mental Health Survey and Incidence Study-2 a lifetime prevalence of 19.1% for any substance use disorder was found.[2] Patients with SUD constitute a large proportion of mental health service users, and are overrepresented in general medical care.[3]

Attention Deficit Hyperactivity Disorder (ADHD) is a major risk factor for the development of substance use disorders,[4-6] either directly[7] or mediated by conduct disorder.[8] Comorbid ADHD has a negative effect on the course of SUD. Patients with both ADHD and SUD become addicted at a younger age, use more substances and are hospitalized more often than SUD patients without ADHD.[9] ADHD is also associated with higher relapse rates after successful addiction treatment.[10] Moreover, treatment studies have consistently shown that pharmacological treatment of ADHD with methylphenidate or atomoxetine is not as effective in ADHD patients with SUD compared to those without this comorbidity.[11-17] Only one study reported a decrease in self-reported ADHD symptoms after treatment in SUD patients.[18] Other treatment strategies such as cognitive behavioural therapy[19] have not been studied in this population.

In order to develop optimal treatment programs for patients with ADHD and SUD, it is important to adequately recognize and diagnose these disorders. This may be complicated by overlapping symptoms, such as effects of drug intoxication or withdrawal.[20] While the prevalence of ADHD among children in the general population is approximately 5%,[21] and in adults around 4%,[22] it is often assumed that the ADHD prevalence in SUD patients is higher. However, prevalence estimates in the literature vary considerably and range from 2% in a study by Hannesdottir and colleagues[23] to 83% in a study by Matsumoto and colleagues.[24] It is currently unclear whether differences in substance of abuse, in ADHD or SUD assessment, or between SUD populations may explain this variation in prevalence estimates. The current study aims to establish a best estimate of the prevalence of comorbid ADHD in adolescents and adults with SUD, using data from high quality studies in a statistical meta- and meta-regression analysis. Differences between studies in terms of patient population, primary substance of abuse, setting and assessment procedure are taken into account. A meta-analytic review of the existing studies to date is important to obtain a more accurate estimate of the comorbidity of ADHD and SUD, as a first step in developing adequate diagnostic and treatment programs for this patient population.

METHOD

Data sources

We conducted a systematic literature search to identify studies reporting on the prevalence of comorbid ADHD in SUD populations using MEDLINE, PsycINFO and EMBASE. Key words

for the search were: ADHD, substance-related disorders (Mesh term MEDLINE), addiction (subject heading in EMBASE), drug abuse, drug dependence, alcohol abuse, alcoholism (key words PsycINFO), comorbidity, and prevalence. English language and human studies were used as limits. Databases were searched from 1966 until January 2010. In addition, cross-references of the retrieved articles were checked.

Study selection

Titles and, if needed, abstracts were screened. All articles reporting on the prevalence of comorbid ADHD within a substance use disorder population were fully assessed by two authors independently (KvE-vO, GvdG) in order to assess eligibility. Differences between these authors were resolved by discussion with the last author (RAS).

The following criteria for inclusion in this meta-analysis were used:

- Studies reporting on the prevalence of comorbid ADHD in a SUD population. Articles with a different focus, but providing information from which the prevalence of ADHD in a SUD population could be extracted, were also included.
- A SUD diagnosis is made in all subjects by means of a validated diagnostic instrument, such as the SCID-I. If specific information on diagnostic procedures for SUD was not available, but the study involved a sample of patients from an addiction treatment centre, we assumed that these patients would qualify for a SUD diagnosis on clinical grounds.
- We included all types of substance use disorders (for example abuse or dependence of alcohol, cocaine, opiates, cannabis, or polysubstance disorders). However, studies reporting on subjects with nicotine dependence as the primary substance of abuse were not included.
- The presence of ADHD was established by means of a (semi) structured diagnostic instrument or a systematic DSM-based clinical interview. Self report questionnaires were not considered to be sufficient for this purpose. Studies were only selected if a clear diagnostic procedure for ADHD was described, and diagnoses were made according to DSM-III or DSM-IV criteria. A lifetime diagnosis of ADHD thus includes a retrospective childhood diagnosis (symptoms starting before age 7), irrespective of symptoms in adulthood. A current diagnosis of ADHD implies a childhood onset ADHD with persisting symptoms in adulthood that currently meet DSM-criteria. Studies in which the age of onset criterion for ADHD was not available were not included.
- Studies on both adults and adolescents were included. Studies on inpatients and outpatients of addiction treatment centres were included (treatment seeking samples), as well as studies based upon community samples (currently not in treatment for addiction problems).

The following exclusion criteria were used:

- Studies reporting on juvenile offenders, as this is a distinct group of adolescents

characterised by delinquent behaviour, which in turn is associated with ADHD.[25-27]

- Studies involving patients in treatment for a psychiatric disorder who had comorbid SUD were also excluded for reasons of sample selection.
- Studies that included different members of the same family, because subjects are not independent in these samples.
- Studies using imputation techniques to estimate the ADHD prevalence.
- Studies lacking information necessary for our analysis.

Data extraction

The following data were extracted from the included studies: sample size, primary substance of abuse, diagnostic procedure for ADHD and SUD, timeframe of ADHD diagnosis (retrospective childhood diagnosis or current diagnosis with persisting symptoms), information on recruitment of the sample, setting and demographic characteristics of the sample, period of abstinence before diagnostic assessment, availability of other informant (for example parent) in ADHD assessment, and information on the prevalence of ADHD.

Data synthesis and statistical analysis

The variable of interest was the prevalence of ADHD in SUD populations. Data on this outcome measure were analysed using Comprehensive Meta-analysis software Version 2.

We expected the results to be quite heterogeneous as we included studies with different demographic characteristics, settings, primary substances of abuse, time frame, and assessment procedure. A test of heterogeneity (Q test) was used to determine whether the differences in prevalence estimates across studies were indeed larger than expected by chance. Heterogeneity was also assessed by the I^2 metric, i.e. the percentage of between study variance due to systematic heterogeneity rather than chance.[28] A random-effects model was used for the meta-analysis, as a fixed effect model is likely to produce misleading results in the presence of significant heterogeneity.[29] In addition, heterogeneity was further explored using a series of meta-regression analyses, in which we evaluated the effect of age, primary substance of abuse, setting and assessment procedure on the prevalence of ADHD in the various SUD populations. These meta-regression analyses were performed using SPSS 17 software with macros provided by Lipsey and Wilson.[30]

The following ***a priori*** defined variables were used for meta-regression: percentage males in the sample, mean age of the sample, setting (treatment seeking versus community), primary substance of abuse, recruitment of the sample (random/consecutive inclusion versus unknown way of inclusion), length of abstinence before diagnosing ADHD (at least 4 days of abstinence or less/unknown), type of adult ADHD diagnosis (lifetime or current), ethnicity (percentage Caucasians in sample), type of diagnostic instrument for ADHD (KSADS, DISC, DICA, systematic clinical interview using DSM criteria, SADSL, DIS or other instrument; abbreviations are explained at the bottom of table 1), and age group of sample (adolescents versus adults). For primary substance of abuse, we created dummy variables

for cocaine, alcohol and opioids, as studies on these substances were the most frequent. If a study sample consisted of for example subjects with cannabis addiction, or a mixed group of SUD patients, the sample was classified as 'other substance' and was used as the reference category relative to the three dummies for cocaine, alcohol and opioids. Dummy variables were also used for the instrument that was used for ADHD diagnosis. The KSADS, DISC, DICA, DSM-list, SADSL and DIS were used as dummy variables for this purpose, with any other instrument as the reference category. Subsequently, a back-step procedure was employed, in which the least significant variable was deleted after every step. Finally, the remaining statistically significant ($p<0.05$) variables were retained in the regression model.

RESULTS

Results of literature search

Figure 1 shows the process of identifying and selecting relevant articles. Searches in MEDLINE, PsycINFO and EMBASE yielded a total of 1040 non-duplicate articles. After screening of titles and abstracts, 59 articles were fully studied by two authors on eligibility, and an additional nine studies were added for eligibility assessment from cross-references. A total of 39 of the 68 studies were excluded for various reasons, which resulted in a final inclusion of 29 articles. A more detailed list of the excluded studies and reasons for exclusion can be obtained from the first author.

Table 1 gives an overview of all selected studies. A total of 29 studies are included, involving 6,689 subjects (4,054 adolescents and 2,635 adults) from 6 countries. 26 studies involved treatment seeking samples. In terms of primary substance of abuse, 5 studies concerned alcohol dependent subjects, 6 studies described cocaine dependent subjects, 3 studies opioid dependent subjects, 1 study involved a cannabis dependent sample, and 14 studies included subjects with various types of SUD (not restricted to one specific substance). Different instruments were used to make ADHD and SUD diagnoses. For the ADHD diagnosis, the K-SADS was the most frequently used diagnostic instrument. For the SUD diagnosis, 9 of the 29 studies did not report the use of a specific instrument, but reported that a diagnosis was made based on a clinical interview using DSM criteria. Among the studies that used a diagnostic instrument for the SUD diagnosis, the SCID was most frequently used. Four studies (14%) reported no specific diagnostic instrument but concerned patients from an addiction treatment center.

ADHD prevalence rates in the included studies ranged from 8% [40] to 44.3% [7] in the adolescent populations and from 9.9% [47] to 54.1% [52] in adult populations. The study by Carroll and Rounsaville[10] reported on two subgroups: a sample of 298 treatment-seeking cocaine abusers (in- and outpatients from a drug abuse clinic), and a community sample of 101 cocaine abusers. The same treatment seeking sample was also reported in the article by Rounsaville and colleagues.[53] Therefore, from Carroll's article we only used the community sample (n=101) in our analysis. The study by Ohlmeier et al.[52] also reports on

Figure 1: Flow diagram study selection.

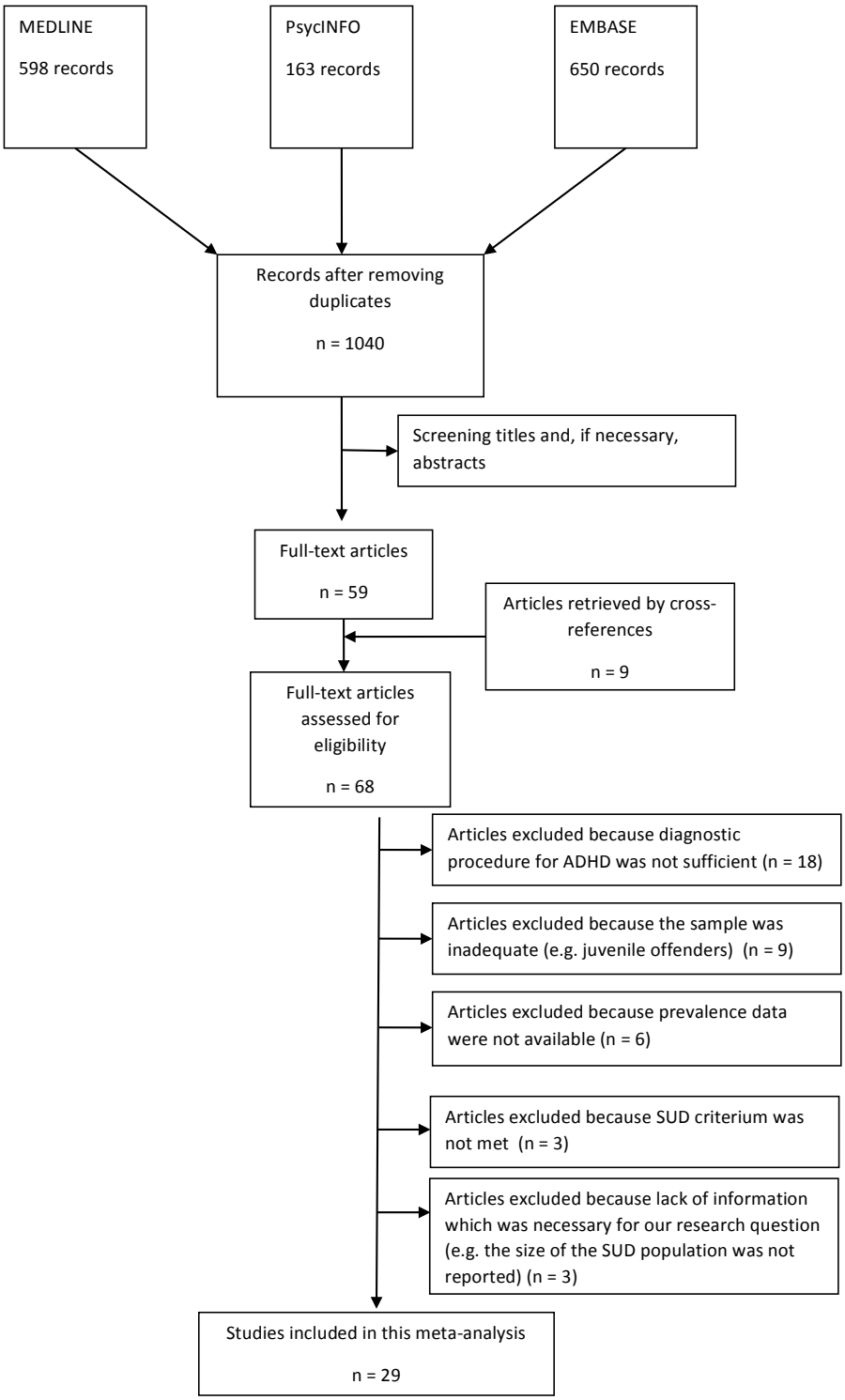


Table 1: Sample and methodological characteristics of included studies.

Study	*N*	*Substance*	*Mean Age*	*Males (%)*	*Ethnicity: Caucasian (%)*	*Instrument for ADHD Diagnosis*	*Instrument for SUD Diagnosis*
Adolescents							
Clark et al., 1997 [31]	133	Alcohol	16.3	59	84	K-SADS	SCID
Garland et al., 2001 [32]	166	Various	-	70	39	DISC	-
Grella et al., 2001 [33]	992	Various	-	69	66	DISC	- [d]
Hovens et al., 1994 [34]	52	Various	16.2	62	92	K-SADS	- [d]
Jainchill et al., 1997 [35]	829	Various	-	76	47	DICA	- [d]
Latimer et al., 2002 [36]	135	Various	15.7	75	83	DICA	- [d]
De Milio, 1989 [37]	57	Various	16.2	70	-	- [c]	-
Molina et al., 2002 [38]	395	Alcohol	16.8	63	83	K-SADS	SCID
Novins et al., 2006 [39]	89	Various	-	65	0	DISC	CIDI-SAM
Stowell et al., 1992 [40]	226	Various	15.9	61	-	K-SADS	SUDDS
Subramaniam and Stitzer, 2009 (A) [41]	94	Opioid	16.9	55	89	DICA-IV	CIDI-SAM
Subramaniam et al., 2009 (B) [42]	74	Various	16.9	65	51	DICA-IV	CIDI-SAM
Szobot et al., 2007 [7]	61	Various	17.8	100	0	K-SADS	MINI
Tarter et al., 1997 [43]	151	Alcohol	16.4	58	84	K-SADS	K-SADS
Tims et al., 2002 [44]	600	Cannabis	-	83	13	GAIN	GAIN
Adults							
Carroll et al., 1993 [10]	101	Cocaine	27.4	69	14	SADS-L	SADS-L
Clure et al., 1999 [45]	136	Various	34.3	76	38	CHAMPS	-
Daigre et al., 2009 [46]	80	Various	36.2	80	91	CAADID	SCID-I
Falck et al., 2004 [47]	313	Cocaine	37.8	59	36	DIS	Urine test
Johann et al., 2003 [48]	314	Alcohol	43.1	83	100	- [c]	CIDI
King et al., 1999 [49]	125	Opioid	37.0	46	36	DIS	SCID-I
Levin et al., 1998 [50]	281	Cocaine	33.7	82	14	KID SCID	SCID-I
Modestin et al., 2001 [51]	101	Opioid	26.0	100	-	- [c]	- [e]
Ohlmeier et al., 2008 [52]							
A [g]	91	Alcohol	46.9	65	-	- [c]	- [d]
B [g]	61	Various	33.0	83	-	- [c]	- [d]
Rounsaville e. a.,1991[53]	298	Cocaine	27.7	69	64	SADS-L	-d
Schubiner et al., 2000[54]	201	Various	35.1	63	79	- [c]	SCID
Tang et al., 2007 [55]	243	Cocaine	39.5	59	37	SSADDA	SSADDA
Wood et al., 1983 [56]	27	Alcohol	-	100	100	Utah criteria	- [d]
Ziedonis et al., 1994 [57]	263	Cocaine	28.0	69	62	SADS-L	- [d]

Note:
Abbreviations: K-SADS, Schedule for Affective Disorders and Schizophrenia for School-Age Children; DISC, Diagnostic Interview Schedule for Children; DICA, Diagnostic Interview for Children and Adolescents; GAIN, Global Appraisal of Individual Needs; SADS-L, Schedule for Affective Disorders and Schizophrenia – Lifetime Version; CHAMPS, Schedule for the Assessment of Conduct, Hyperactivity, Anxiety, Mood and Psychoactive Substances; CAADID, Conners' adult ADHD Diagnostic Interview for DSM-IV; DIS, Diagnostic Interview Schedule for DSM-IV; KIDSCID, (unpublished instrument) Structured Clinical Instrument for DSM-IV Axis I Disorders for Children and Adolescents; SSADDA, Semi-Structured Assessment for Drug Dependence and Alcoholism; SCID I, Structured Clinical Interview for Diagnostic Statistical Manual – IV for Axis I disorders; CIDI-SAM, Composite International Diagnostic Interview – Substance Abuse Module; SUDDS, Substance Use Disorders Diagnostic Schedule; MINI, Mini International Neuropsychiatric Interview.

Recruit-ment	*Setting*	*Abstinence & Diagnosis* [a]	*Other informant (e.g. parent)*	*ADHD Prevalence (%)*	*Timeframe ADHD diagnosis*[f]
- [b]	Treatment	1	Yes	28.6	
Random	Treatment	-	Yes	21.1	
Consecutive	Treatment	-	No	13	
-	Treatment	1	Yes	31	
Consecutive	Treatment	-	No	24.6	
Consecutive	Treatment	-	Yes	40	
Consecutive	Treatment	1	Yes	14	
-	Treatment	-	Yes	28.6	
Consecutive	Treatment	1	No	18	
Consecutive	Treatment	1	No	8	
-	Treatment	-	No	33	
-	Treatment	-	No	39	
-	Community	2	Yes	44.3	
-	Treatment	1	Yes	19.9	
Consecutive	Treatment	-	No	38	
					Timeframe[f]
-	Community	1	No	23.8	Lifetime
-	Treatment	1	No	15	Current
-	Treatment	-	No	20	Current
Consecutive	Community	2	No	9.9	Lifetime
-	Treatment	-	No	21.3	Current
Consecutive	Treatment	2	Yes, but not in all patients.	19	Lifetime
Partly random	Treatment	1	Yes	10	Current
-	Treatment	-	No	11	Lifetime
-	Treatment	1	No	23.1	Lifetime
Consecutive	Treatment	1	No	54.1	Lifetime
Random	Treatment	1	No	34.9	Lifetime
-	Treatment	1	No	24	Current
Consecutive	Treat+Com	-	No	10.1	Lifetime
Consecutive	Treatment	-	Yes	33	Current
	Treatment	1	No	34.6	Lifetime

[a] The moment of diagnosing ADHD is coded (1) if patients were abstinent at least 4 days before assessment, and coded (2) if the length of abstinence was shorter than 4 days.
[b] '-' refers to data not reported.
[c] ADHD diagnosis was made according to DSM criteria, but no specific instrument was reported.
[d] SUD diagnosis was made according to DSM III or IV criteria, but no specific instrument was reported.
[e] SUD diagnosis was made according to ICD-10 criteria, but no specific instrument was reported.
[f] For studies reporting on adults, information is provided on whether the ADHD prevalence is 'lifetime' (retrospective childhood diagnosis without mentioning of current symptoms) or 'current' (childhood onset ADHD with persisting symptoms in adulthood). When studies mention prevalence rates on lifetime as well as current diagnoses, we used prevalence rates for current diagnoses.
[g] The study by Ohlmeier ***et al*** consists of 2 samples, namely an alcohol dependent and a drug dependent sample respectively.

two samples: 91 alcohol-dependent inpatients, and 61 substance-dependent inpatients. In our review, these samples are indicated with A and B respectively. This splitting results in 30 entries instead of 29 entries (reported in the flow chart) in table 1. Subramaniam and colleagues[41, 42] studied several samples of substance abusing patients, and reported on the prevalence of ADHD and other disorders. In the article indicated with A,[41] the authors report on a prescription opioids and heroin using sample. In another article, indicated with B,[42] the authors report on the same opioid dependent sample but also on alcohol and cannabis dependent patients. From the latter article, we only used data from the alcohol and/ or cannabis dependent patients to prevent double counting. Finally, the study by Falcket al.[47] reports on a community sample of crack-cocaine abusers. Diagnostic procedures to confirm dependence or abuse were not available in this study, but crack use was confirmed by urine tests.

Results of the meta-analysis

Data on ADHD prevalence in the 29 included studies were pooled, yielding an overall prevalence estimate of 23.1% (C.I: 19.4% – 27.2%) with I^2=92.2%, Q=372.6; df = 29; p<0.05, indicating substantial heterogeneity (see figure 2).

Analyses were also performed for adolescents and adults separately. Results showed that overall ADHD prevalence in adolescents was 25.3% (C.I. 20.0 – 31.4 %, I^2= 93.2%), and that overall ADHD prevalence in adults was 21.0% (C.I. 15.9 – 27.2 %, I^2= 91.3%) with I^2 parameters still indicating substantial heterogeneity. We also analysed subgroups of treatment seeking and community samples in adolescent and adult populations. In adolescent populations, only one study used a community sample (Szobot et al.);[7] in this study a prevalence of 44.3% was found (C.I. 32.4 – 56.9%). All the other studies on adolescents used treatment seeking samples; pooling of these studies resulted in an ADHD prevalence of 24.2 % (C.I. 19.0 – 30.4%). In adult populations, 2 studies had been performed with community samples, resulting in a pooled ADHD prevalence estimate of 15.5% (C.I. 6.2 – 33.8%). Twelve studies focussed on treatment seeking patients, and the ADHD prevalence in this subgroup was 23.3% (C.I. 17.7 – 30.1 %).

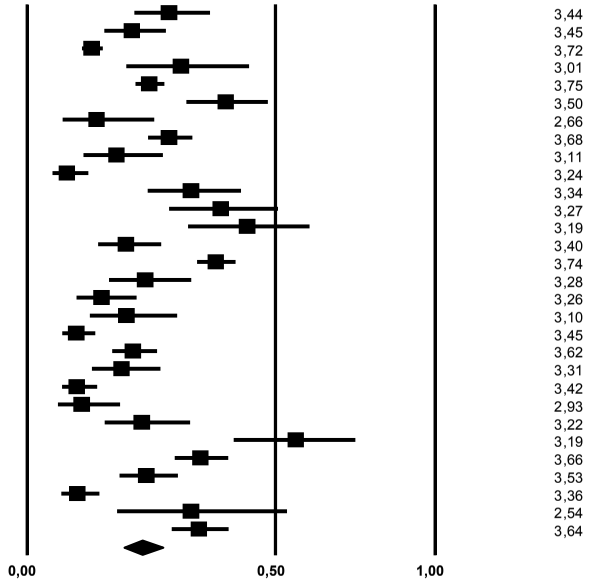
Results of additional analyses

A sensitivity analysis was performed to assess how the results were influenced if one study was omitted at a time. The resulting prevalence estimates ranged from 22.3 % (C.I. 18.7 – 26.3%) if the study by Ohlmeier[52] (part B) was omitted, to 23.8% (C.I. 20.1 – 28.0 %) if the study by Stowell and Estroff [40] was omitted, indicating no disturbing effects on the overall prevalence estimate of any one study.

We also ran the analysis using only the 14 studies specifically reporting a random sample or consecutive inclusion for the ADHD prevalence diagnostic procedure. The other 15 studies did not report on how inclusion of their sample was realized. Possibly, this could have led to selecting subjects with a high risk of ADHD, resulting in overestimating ADHD prevalence. However, ADHD prevalence in this analysis remained 23.1% (C.I. 17.8 – 29.3%, I^2= 94.4%).

Figure 2: Prevalence of ADHD in SUD populations.

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	ADHD/ Total sample	Relative weight
Clark et al	0,286	0,216	0,368	-4,768	0,000	38 / 133	3,44
Garland et al	0,211	0,156	0,280	-6,933	0,000	35 / 166	3,45
Grella et al	0,130	0,110	0,152	-20,135	0,000	129 / 992	3,72
Hovens et al	0,310	0,200	0,447	-2,668	0,008	16 / 52	3,01
Jainchill et al	0,246	0,218	0,276	-13,889	0,000	204 / 829	3,75
Latimer et al	0,400	0,321	0,485	-2,308	0,021	54 / 135	3,50
de Milio	0,140	0,072	0,256	-4,756	0,000	8 / 57	2,66
Molina et al	0,286	0,244	0,333	-8,217	0,000	113 / 395	3,68
Novins et al	0,180	0,113	0,274	-5,496	0,000	16 / 89	3,11
Stowell et al	0,080	0,051	0,123	-9,961	0,000	18 / 226	3,24
Subramaniam A	0,330	0,243	0,431	-3,229	0,001	31 / 94	3,34
Subramaniam B	0,390	0,286	0,505	-1,877	0,061	29 / 74	3,27
Szobot et al	0,443	0,324	0,569	-0,888	0,374	27 / 61	3,19
Tarter et al	0,199	0,143	0,270	-6,832	0,000	30 / 151	3,40
Tims et al	0,380	0,342	0,420	-5,820	0,000	228 / 600	3,74
Carroll et al	0,238	0,165	0,331	-4,980	0,000	24 / 101	3,28
Clure et al	0,150	0,099	0,220	-7,223	0,000	20 / 136	3,26
Daigre et al	0,200	0,126	0,302	-4,960	0,000	16 / 80	3,10
Falck et al	0,099	0,070	0,137	-11,669	0,000	31 / 313	3,45
Johann et al	0,213	0,171	0,262	-9,482	0,000	67 / 314	3,62
King et al	0,190	0,130	0,268	-6,360	0,000	24 / 125	3,31
Levin et al	0,100	0,070	0,141	-11,050	0,000	28 / 281	3,42
Modestin et al	0,110	0,062	0,187	-6,574	0,000	11 / 101	2,93
Ohlmeier et al A	0,231	0,156	0,328	-4,835	0,000	21 / 91	3,22
Ohlmeier et al B	0,541	0,416	0,661	0,640	0,522	33 / 61	3,19
Rounsaville et al	0,349	0,297	0,405	-5,130	0,000	104 / 298	3,66
Schubiner et al	0,240	0,186	0,304	-6,979	0,000	48 / 201	3,53
Tang et al	0,101	0,069	0,146	-10,269	0,000	25 / 243	3,36
Wood et al	0,330	0,181	0,523	-1,730	0,084	9 / 27	2,54
Ziedonis et al	0,346	0,291	0,405	-4,912	0,000	91 / 263	3,64
Pooled mean	0,231	0,194	0,272	-10,677	0,000		



For each study ADHD prevalences (displayed as event rates), 95% confidence intervals (95% CI), numbers of ADHD cases, total sample sizes and weights are presented. At the bottom of the figure, the pooled estimate is presented.

Finally, we performed an analysis including only the 14 studies in which the diagnostic procedure was performed after a period of at least 4 days of abstinence. Again, overall ADHD prevalence in this subgroup was very similar to the overall estimate for all studies: 22.6% (C.I. 17.2 – 29.1 %, I^2= 90.0%).

Results of the meta-regression analysis

We performed a series of meta-regression analyses to evaluate the effect of age, gender, setting, primary substance of abuse, recruitment method, abstinence duration, time-frame, ethnicity, and assessment procedure on the prevalence of ADHD in SUD populations. An initial association with the prevalence of ADHD was observed for cocaine as the primary substance of abuse, and for assessment of ADHD with the SADSL. After a back-step procedure, in which the least significant variable was deleted after every step, three statistically significant variables were retained in the regression model: ADHD assessment with the DICA, ADHD with SADS-L (both resulting in higher rates of comorbid ADHD than assessment with other ADHD interviews), and cocaine as the primary substance of abuse (resulting in a lower rate of ADHD than in subjects with other primary substances of abuse). These three variables together explained 38.0% of the total variance between studies (see table 2). After adjustment for these variables, the overall ADHD prevalence remained unchanged (23.1%), but the confidence interval became narrower and ranged from 19.9% to 26.7%.

Table 2: Meta-Regression analysis of study variables significantly associated with ADHD prevalence in SUD populations (N = 30).

	B	SE	-95% CI	+95% CI	Z	P	Beta
Constant	-1.2240	.1134	-1.4462	-1.0017	-10.7929	.0000	.0000
Cocaine	-.9734	.3061	-1.5735	-.3734	-3.1797	.0015	-.6166
DICA	.5355	.2682	.0098	1.0613	1.9965	.0459	.2889
SADS-L	1.4084	.3968	.6306	2.1861	3.5492	.0004	.6798

Note.
Mean ES = -1.2015, R^2 = .3800
DICA: Diagnostic Interview for Children and Adolescents
SADS-L: Schedule for Affective Disorders and Schizophrenia – Lifetime version

DISCUSSION

In this statistical meta-analysis, we provide a best estimate of ADHD prevalence in SUD populations, based upon all currently available studies of sufficient quality and adjusted for a range of variables potentially affecting prevalence. Results indicate that the overall

prevalence is approximately 23%, irrespective of age and gender, ethnicity, duration of abstinence, time-frame, and setting. A series of meta-regression analyses showed that the prevalence of ADHD is significantly lower in subjects with cocaine as their primary substance of abuse, whereas the prevalence is higher in studies with a diagnosis of ADHD based on the DICA or the SADS-L.

To our knowledge, this is the first meta-analytic review on the subject. We were able to include as many as 29 studies and a total of 6,689 subjects. Sensitivity analyses showed that the results were stable when omitting one study at a time. Also, results were not altered when analyzing a subgroup of studies that considered a period of abstinence before the ADHD assessment, or when analyzing a subgroup of studies that provided more detailed information on their sampling procedure.

The results that we found are relevant for the treatment of addiction and its psychiatric comorbidities. As almost one in every four SUD patients also meets ADHD diagnostic criteria, it is important to implement adequate screening and case-finding procedures to identify those patients. Moreover, the need for developing effective treatment programs for patients with SUD and comorbid ADHD is emphasized by these results.

Interestingly, we did not observe a significant association between clinical variables such as proportion of males in the sample, mean age of the sample, or study setting and the prevalence of comorbid ADHD, so the wide variation in prevalence estimates that we found in the literature does not seem to be explained by the differences in patient populations. Only diagnostic instrument and cocaine as primary substance of abuse appeared to be related to the prevalence estimate in our analyses. It should be noted that in community samples both SUD and ADHD are more frequently diagnosed in males than in females. However, within a SUD population, ADHD seems to be equally prevalent among males and females. Although tentative, one might suggest that ADHD and SUD represent the outcome of a final common pathway with an important overlap in risk factors such as genetic vulnerability[58] and maternal smoking during pregnancy[59, 60] in both males and females.

Another interesting finding is that a primary cocaine use disorder was associated with lower ADHD prevalence. Although it has been reported that patients with ADHD are likely to choose cocaine to self-medicate symptoms of ADHD,[61] several other studies did not find a preference of cocaine in ADHD patients.[45, 4] A possible explanation for our finding could be that sedating substances like alcohol and cannabis are more effective in alleviating ADHD symptoms. It should be noted that all the studies in which cocaine was the primary drug of abuse were conducted in adult populations. In general population studies, ADHD prevalences are usually lower in adults than in adolescents.[62] The lower ADHD prevalence in cocaine abusing populations could thus be a function of age. Still, this age difference was not found in our pooled data on SUD patients so this seems unlikely. Furthermore, although we consider it useful to group studies according to primary drug of abuse, we realise that in practice patients may use more drugs at the same time.

A final variable explaining some of the heterogeneity in the prevalence of ADHD in SUD

populations is the assessment procedure and instrument used for the diagnosis of ADHD. Although only studies with adequate diagnostic instruments were included in this meta-analysis, information on the timing of the ADHD assessment was often limited. Timing of diagnostics can be crucial, as symptoms of substance intoxication or withdrawal can be easily misinterpreted as ADHD symptoms. An adequate period of abstinence before diagnostic assessment is therefore considered to be of major importance. In our analysis, the ADHD prevalence in subjects with SUD was not altered when we restricted the analyses to the 14 studies which explicitly stated that they had performed the ADHD diagnostic procedure after a period of at least four days of abstinence.

We found higher rates of ADHD in studies using the SADS-L in adults or the DICA in adolescents. Due to the absence of direct comparisons, it is not possible to say whether studies using the SADS-L or the DICA overestimate the prevalence of ADHD or whether studies using other instruments underestimate the prevalence of ADHD. The only indication for the validity of the DICA we found in the literature is a high agreement between trained lay interviewers and child psychiatrists using the DICA in a general population sample.[63]

The current study has both strengths and limitations. The most important strengths are the large number of included studies and subjects, the strict inclusion criteria, and the state-of-the-art analysis of the data using meta-regression. There are also limitations that must be considered when interpreting the results. First, studies among different groups of clinical patients, such as adults and adolescents and patients with different types of SUD, were included in this review. However, this clinical heterogeneity was accommodated for by using a random-effects model for meta-analysis and by incorporating these variables in meta-regression analyses. Using this strategy, 38.0% of the variance between studies could be accounted for. Second, different instruments were used to evaluate ADHD, and 6 studies used a DSM-IV based clinical interview instead of a semi-structured instrument. This heterogeneity was also explored in meta-regression analyses. Using a clinical interview for diagnosing ADHD was not associated with statistically significant differences in prevalence in meta-regression. Repeating the random-effects meta-analysis without these 6 studies, we found the same prevalence, albeit with a slightly wider confidence interval. Third, only studies meeting DSM criteria for ADHD were included, i.e. a minimum of 6 symptoms is required as well as having symptoms before the age of 7. These criteria, especially age at onset, are subject of debate.[64, 65] It is argued that early age of onset may not be necessary for a diagnosis of adult ADHD, and this criterion is likely to be adjusted in DSM5 (http://dsm5.org). As an accurate ADHD diagnosis is more challenging in the presence of SUD-related symptoms such as restlessness, impulsivity and concentration problems, we choose to hold on to the current DSM-IV criterion of early onset. Due to this relatively conservative strategy the rates provided in this study are accurate but may provide an underestimation rather than an overestimation of the actual ADHD prevalence in SUD patients. The fact that information from family members was not always part of the assessment procedure may have led to underestimation of the presence of ADHD symptoms as well, especially in the studies with adolescents who tend to have relatively poor insight into their ADHD

symptoms and typically underreport their symptoms.[66] Also in the included studies with adults, information of a family member was often not available. A study by Murphy and Schachar[67] examined this issue and found high correlations between subject and observer (parent and partner) ratings of ADHD symptoms in adults.

It is interesting to know if treatment of ADHD influences SUD symptoms. In a study by Biederman and colleagues[68] in which children with ADHD were followed up into young adulthood, no evidence was found that stimulant treatment affects the risk of subsequent SUD, but in two other prospective studies,[69, 70] beneficial effects were found of an early start of methylphenidate treatment of children with ADHD in terms of reducing the risk of subsequent SUD. Little is known about the effect of ADHD treatment on adult patients who already developed SUD, but in the medication trials that have been performed until now, no clear effect of medication treatment on substance use was shown.[12, 14, 16, 17] The only exception to this was a study among cocaine dependent ADHD patients receiving methylphenidate,[13] in which a reduction of ADHD symptoms through medication was associated with a reduction in cocaine use.

Overall, this meta-analysis may contribute to the awareness that ADHD comorbidity is frequently present in substance-abusing populations, irrespective of age, gender, ethnicity and setting. Given the clinical importance and the limited efficacy of current treatment approaches, both recognition and further study of interventions for this type of comorbidity are urgently needed.

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