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Psychiatric comorbidity in treatment-seeking substance use disorder patients with and without attention deficit hyperactivity disorder: results of the IASP study

Katelijne van Emmerik-van Oortmerssen[1,2,3,*], **Geurt van de Glind**[2,4,*], **Maarten W. J. Koeter**[2], **Steve Allsop**[5], **Marc Auriacombe**[6], **Csaba Barta**[7], **Eli Torild H. Bu**[8], **Yuliya Burren**[9], **Pieter-Jan Carpentier**[10], **Susan Carruthers**[5], **Miguel Casas**[11], **Zsolt Demetrovics**[12], **Geert Dom**[13], **Stephen V. Faraone**[14,15], **Melina Fatseas**[6], **Johan Franck**[16], **Brian Johnson**[14,15], **Máté Kapitány-Fövény**[12,17], **Sharlene Kaye**[18], **Maija Konstenius**[16], **Frances R. Levin**[19], **Franz Moggi**[9,20], **Merete Møller**[21], **J. Antoni Ramos-Quiroga**[11], **Arild Schillinger**[21], **Arvid**

Correspondence to: Katelijne van Emmerik-van Oortmerssen, Research Department, Arkin, Klaprozenweg 111, 1033 NN Amsterdam, the Netherlands. katelijne.van.oortmerssen@arkin.nl.
*The first two authors contributed equally to this study.
†The last two authors contributed equally to this study
‡See Acknowledgements section for members of the IASP research group.

Declaration of interests

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Skutle[8], **Sofie Verspreet**[13], **IASP research group**[‡], **Wim van den Brink**[2,†], and **Robert A. Schoevers**[3,†]

[1]Arkin Mental Health and Addiction Treatment Center, Amsterdam, the Netherlands [2]Amsterdam Institute for Addiction Research, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands [3]Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands [4]Trimbos-Instituut and ICASA Foundation, Utrecht, the Netherlands [5]National Drug Research Institute/Curtin University of Technology, Perth, Western Australia, Australia [6]Labotatrie Département d'addictologie, Université de Bordeaux, Bordeaux, France [7]Institute of Medical Chemistry, Molecular Biology and Pathobiochemistry, Semmelweis University, Budapest, Hungary [8]Bergen Clinics Foundation, Bergen, Norway [9]University Hospital of Psychiatry, Bern, Switzerland [10]Reinier van Arkel groep, 's-Hertogenbosch, the Netherlands [11]Servei de Psiquiatria, Hospital Universitari Vall d'Hebron, CIBERSAM, Department of Psychiatry, Universitat Autònoma de Barcelona, Barcelona, Spain [12]Institute of Psychology, Eötvös Loránd University Budapest, Hungary [13]Collaborative Antwerp Psychiatry Research Institute (CAPRI, UA), PC Alexian Brothers, Boechout, Belgium [14]Department of Psychiatry SUNY Upstate Medical University, Syracuse, NY, USA [15]Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA [16]Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden [17]Nyírő Gyula Hospital Drug Outpatient and Prevention Center, Budapest, Hungary [18]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia [19]Columbia University/the New York State Psychiatric Institute, New York, NY, USA [20]Department of Psychology, University of Fribourg, Fribourg, Switzerland [21]Department for Substance Abuse Treatment, Ostfold Hospital Trust, Fredrikstad, Norway

Abstract

Aims—To determine comorbidity patterns in treatment-seeking substance use disorder (SUD) patients with and without adult attention deficit hyperactivity disorder (ADHD), with an emphasis on subgroups defined by ADHD subtype, taking into account differences related to gender and primary substance of abuse.

Design—Data were obtained from the cross-sectional International ADHD in Substance use disorder Prevalence (IASP) study.

Setting—Forty-seven centres of SUD treatment in 10 countries.

Participants—A total of 1205 treatment-seeking SUD patients.

Measurements—Structured diagnostic assessments were used for all disorders: presence of ADHD was assessed with the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID), the presence of antisocial personality disorder (ASPD), major depression (MD) and (hypo)manic episode (HME) was assessed with the Mini International Neuropsychiatric Interview-Plus (MINI Plus), and the presence of borderline personality disorder (BPD) was assessed with the Structured Clinical Interview for DSM-IV Axis II (SCID II).

Findings—The prevalence of DSM-IV adult ADHD in this SUD sample was 13.9%. ASPD [odds ratio (OR) = 2.8, 95% confidence interval (CI) = 1.8–4.2], BPD (OR = 7.0, 95% CI = 3.1–15.6 for alcohol; OR = 3.4, 95% CI = 1.8–6.4 for drugs), MD in patients with alcohol as primary substance of abuse (OR = 4.1, 95% CI = 2.1–7.8) and HME (OR = 4.3, 95% CI = 2.1–8.7) were all more prevalent in $ADHD^+$ compared with $ADHD^-$ patients ($P < 0.001$). These results also indicate increased levels of BPD and MD for alcohol compared with drugs as primary substance of abuse. Comorbidity patterns differed between ADHD subtypes with increased MD in the inattentive and combined subtype ($P < 0.01$), increased HME and ASPD in the hyperactive/impulsive ($P < 0.01$) and combined subtypes ($P < 0.001$) and increased BPD in all subtypes ($P < 0.001$) compared with SUD patients without ADHD. Seventy-five per cent of ADHD patients had at least one additional comorbid disorder compared with 37% of SUD patients without ADHD.

Conclusions—Treatment-seeking substance use disorder patients with attention deficit hyperactivity disorder are at a very high risk for additional externalizing disorders.

Keywords

ADHD; antisocial personality disorder; bipolar disorder; borderline personality disorder; comorbidity; depression; substance use disorder

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a highly comorbid disorder in patients with substance use disorders (SUD) [1,2]. Moreover, both SUD and ADHD are associated with various other comorbid conditions. SUD are reported to co-occur with a variety of other disorders, with mood and anxiety disorders, borderline personality disorder (BPD) and antisocial personality disorder (ASPD) being the most frequently reported in the literature [3,4]. ADHD is also associated with other comorbid conditions [5,6]. Few studies have investigated the comorbidity of patients with both ADHD and SUD, reporting a consistently higher prevalence of additional psychiatric disorders in SUD patients with ADHD ($ADHD^+$) compared to SUD patients without ADHD ($ADHD^-$) [7–10].

Overall, these studies show that ADHD and SUD independently confer an enhanced risk of comorbidity with mood, anxiety and personality disorders, and that a combination of ADHD and SUD results in an even higher risk. This pattern of multiple co-occuring mental disorders is associated with severe emotional and interpersonal problems in the daily life of patients and constitutes a serious challenge for clinicians. Moreover, SUD patients with ADHD are reported to have worse treatment outcomes for both SUD [11] and ADHD [12]. More knowledge about the complex patterns of co-occurring mental disorders in SUD patients with and without ADHD is important, because different patterns of comorbidity may be partly responsible for lower treatment retention and worse outcomes in patients with SUD and ADHD compared to those with SUD alone.

The main limitation of the currently available studies is that little or no attention is given to possible differences in comorbidity patterns in specific subgroups of SUD patients with and without ADHD due to the relatively small sample sizes of these studies. For example, the DSM-IV subtypes of ADHD (predominately inattentive, predominately hyperactive/

impulsive, combined) seem to be associated with different comorbidity patterns in adolescent [13–15] and adult ADHD [16–19] patients. No gender differences in comorbidity were reported in adult ADHD patients [17]. However, it is unknown whether or not these subgroups (ADHD types, gender) show different comorbidity patterns in a population of adult SUD patients with comorbid ADHD. Moreover, it is unknown whether different comorbidity patterns are associated with differences in the primary substance of abuse (alcohol versus illicit drugs) in this population. This information on comorbidity patterns in different subgroups of SUD patients with adult ADHD is needed for the development of targeted and integrated treatment interventions, which focus not only on addiction problems, but also take into account other disorders that are present. Although there are sporadic data on this subject in earlier papers, this is the first large-scale study to investigate the comorbidity patterns in SUD patients with and without adult ADHD.

The main objective of this paper is to determine comorbidity patterns in adult treatment seeking SUD patients with and without comorbid ADHD with special emphasis on possible differences in comorbidity patterns among SUD patients with different ADHD subtypes, taking into account possible differences related to gender and primary substance of abuse (alcohol versus illicit drugs). Both internalizing and externalizing disorders will be studied, focusing on current major depressive disorder (MD), current (hypo)manic episode (HME), antisocial personality disorder (ASPD) and borderline personality disorder (BPD).

METHODS

This study was part of the International ADHD in Substance use disorders Prevalence study (IASP study) conducted by the ICASA research group (International Collaboration on ADHD and Substance Abuse [20]. In this two-stage study, a total of 3558 treatment seeking SUD patients from 10 countries were screened for ADHD (screening phase). At a selection of study sites, all patients (both screen-positive and screen-negative) were asked to participate in an extensive psychiatric interview which took place within a few weeks after screening (full assessment phase). During this full assessment, all patients were evaluated for the presence of ADHD, SUD and other comorbid psychiatric disorders by trained professionals. For a detailed description of the IASP study, the reader is referred to van de Glind *et al*. [21]. In this study we provide a short summary of the methodology.

Participants

In the IASP study, patients aged 18–65 years referred consecutively to participating addiction treatment centres in the period July 2009 to November 2011 were invited to participate. A total of 47 centres in 10 countries (Australia, Belgium, France, Hungary, the Netherlands, Norway, Spain, Sweden, Switzerland and the United States) participated in the screening phase, including both in-patient and out-patient treatment facilities serving both alcohol and/or illicit drug dependent patients. Seven of these countries (France, Hungary, the Netherlands, Norway, Spain, Sweden and Switzerland) also participated in the full assessment phase. There were no formal exclusion criteria for participation, but for practical reasons some patients could not participate in the study (e.g. incapacity to complete the screening questionnaire due to limited literacy, acute intoxication or acute deterioration of a

serious psychiatric or somatic disorder). Only patients with all measures of the full assessment phase were included in the current comorbidity study.

A total of 3558 participants were included in the screening phase of the IASP study [21]. Of these, 1276 completed at least the CAADID in the full assessment phase. Both ADHD screen-positive cases and ADHD screen-negative cases were included in the sample. For different reasons, 71 participants had missing values on one or more of the other instruments of the full assessment, resulting in 1205 patients with a complete set of assessments. The analyses in this report are based on these 1205 patients. There were no significant differences between the study population (n = 1205) and the patients who dropped out (n = 1392) in terms of gender or in primary substance of abuse. However, the study sample was slightly older than the patients who dropped out in two of the countries: Norway (mean age difference 3.1 years, P = 0.003) and Spain (mean age difference 3.3 years, P < 0.001).

Detailed information on demographics, primary substance of abuse and recruitment setting is provided in the Supporting information (see Supporting information Table S1 available online), and can be found in Van de Glind *et al*. (in press) [21].

Design and procedure

The IASP study was approved by the regional medical– ethical committees of all participating centres. All participants provided written informed consent prior to participation. They did not receive financial compensation, except for Australia, where participants received AUD $20 remuneration for associated costs. In the screening phase of the study, a short questionnaire was completed covering demographic information, information on substance use and an ADHD screener (all self-report). All participants were then invited to take part in the full assessment phase, which took place at the addiction treatment centre within 2–4 weeks after the screening, and included a face-to-face diagnostic evaluation for ADHD, SUD, current and life-time major depression, current and life-time (hypo)mania, BPD and antisocial personality disorder (APD). Patients had preferably reached abstinence by that time, but also in the case of ongoing substance use the diagnostic evaluation was performed.

Measures

For a detailed description and indications regarding the reliability and validity of the assessment instruments, the reader is referred to the methods publication of the IASP study [21].

The Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) [22] was used for the diagnosis of DSM-IV ADHD. The CAADID is an extensive semi-structured interview addressing the presence of ADHD, specifically requiring the presence of childhood ADHD symptoms before the onset of alcohol/drug use as well as the presence of adult ADHD symptoms. It also has additional criteria regarding age of onset of ADHD symptoms (before age 7 years), pervasiveness of ADHD symptoms in multiple domains, the presence of ADHD symptom-related impairments and the presence of any other disorders (including SUD) that may account more effectively for the presence of ADHD symptoms. Modules of

the Mini International Neuropsychiatric Interview (MINI Plus) [23] were used to assess MD, HME and ASPD. The presence of BPD was evaluated with the relevant section of the Structured Clinical Interview for DSM-IV Axis II (SCID II) [24,25]. All diagnostic instruments were administered by interviewers trained in the assessment instruments.

In analysing the data on MD, no distinction was made between major depressive episode, substance-induced major depressive episode or major depressive episode following bereavement: all were subsumed under MD. Similarly, (hypo)mania also included substance-induced (hypo)mania. Data are presented here for current MD and current HME only.

Data analysis

Because of the three-level sampling structure, subjects within site within country, we used two-level multilevel analyses. Although a three-level structure seemed warranted, goodness-of-fit comparisons revealed that a three-level model did not fit the data better than a two-level model. Goodness-of-fit was assessed with the Deviance Information Criterion (DIC) [26] based on Markov Chain Monte Carlo modelling, with Metropolis–Hastings sampling and 50 000 iterations. DIC is a generalization of the Akaike's information criterion.

Differences in demographic characteristics and primary substance of abuse were tested with a two-level logistic regression analysis with site as level two variable and random slope, with the exception of the differences in age, which was tested with a two-level linear regression analysis with site as level two variable and random slope. The relation between presence of ADHD and the presence of a specific comorbid disorder and the relation between ADHD subtype and the presence of a specific comorbid disorder was assessed with two-level logistic regression analysis, with site as level two variable and random slope, comorbid disorder as dependent variable, ADHD (yes/no) as independent variable and age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs) as covariates. To assess whether gender and/or primary substance of abuse modified the relation between ADHD and a specific comorbid disorder, we added the gender × ADHD and primary substance of abuse × ADHD interaction to the logistic regression model. When the regression coefficient for an interaction term was statistically significant, results were stratified by categories of the effect modifier. The relation between presence of ADHD and number of comorbid disorders was assessed by a two-level ordinal regression model, with site as level two variable and random slope.

For all analyses, $P < 0.05$ was regarded as statistically significant. To correct for multiple testing of four disorders, we used Bonferroni correction (by dividing the significance threshold value by the number of tests).

In the current report, we provide unweighted estimates of the prevalence rates, which may be slightly different from the weighted estimates of ADHD in the IASP paper on ADHD prevalence [2].

All statistical analyses were conducted with MLwiN version 2.27 (Centre for Multilevel Modelling, University of Bristol, UK).

RESULTS

To decide whether a two- or three-level model was warranted, we compared the DIC for the models used for the main analyses (Table 2): for depression DIC two-level model 1113.98 and three-level model 1113.83; for (hypo)mania DIC two-level model 456.223 and three-level model 456.06; for ASPD, DIC two-level model 1122.49 and three-level model 1122.80; and for BPD DIC two-level model 893.88 and three-level model 893.64. The differences were marginal; consequently, we decided to use the more parsimonious two-level approach.

Study population characteristics

Adult ADHD was present in 13.9% of these treatment-seeking SUD patients. Table 1 shows that the majority of the patients were male (73.1% in the $ADHD^-$ group; 75.6% in the $ADHD^+$ group) with a mean age of 40.7 [standard deviation (SD) 11.3] years for the $ADHD^-$ group and a significantly younger mean age of 35.6 years (SD 9.6) in the $ADHD^+$ group. In the $ADHD^+$ group, significantly more subjects were single ($P < 0.001$), fewer were married or living with a partner ($P < 0.05$) and fewer were divorced ($P < 0.05$). Significantly more subjects in the $ADHD^+$ group reported stimulants and cannabis as their primary drug of abuse, and significantly fewer subjects reported alcohol as their primary substance of abuse (all $P < 0.001$).

Comorbid disorders

Table 2 shows that all comorbid disorders were present more frequently in the $ADHD^+$ group compared to the $ADHD^-$ group, with an exception for current depression in SUD patients with illicit drugs as their primary substance of abuse. The effect of ADHD on comorbid disorders was not modified by gender (no significant gender × ADHD interaction term). When Bonferroni correction for multiple testing was applied, all significant results in Table 2 remained statistically significant.

Overall, 37% of the $ADHD^-$ group had at least one comorbid disorder, while 75% of the $ADHD^+$ group had at least one additional comorbid disorder. Table 3 shows the number of comorbid disorders for SUD patients with and without ADHD. The patients with ADHD had an increased risk of having one or more comorbid disorders [odds ratio (OR) = 3.5 (2.5–4.9), $P < 0.001$ $\sigma 2u = 0.495$ (0.212)].

Comorbidity in subtypes of ADHD

Finally, analyses were repeated to estimate the proportion of patients with comorbid disorders in patients with the different subtypes of current ADHD. Table 4 shows the results for patients with the inattentive, hyperactive/ impulsive and combined subtypes of ADHD. BPD remained significantly more prevalent in SUD patients with all types of ADHD compared to SUD patients without ADHD. HME and ASPD were more prevalent in patients with the hyperactive/impulsive or combined subtype of ADHD, but not in patients with the inattentive ADHD subtype. MD was more prevalent in SUD patients with the inattentive and combined subtype of ADHD, but not in patients with the hyperactive/impulsive type, compared to SUD patients without ADHD.

DISCUSSION

Main findings

This study shows clearly that additional comorbid disorders are far more prevalent in treatment-seeking SUD patients with ADHD than in treatment-seeking SUD patients without ADHD. This applies to all four investigated disorders; namely, ASPD, BPD, HME and MD, with ORs ranging from 2.1 for MD to 7.0 for BPD in SUD patients with alcohol as the primary substance of abuse. Comorbidity patterns differed between ADHD subtypes with increased MD in the inattentive and combined subtype, increased ASPD and HME in the hyperactive/ impulsive and combined subtypes and increased BPD in all three types. These results also show different comorbidity patterns for alcohol versus drugs as the primary substance. The vast majority (75%) of SUD patients with ADHD had at least one additional comorbid disorder, compared to 'only' 37% for the SUD patients without ADHD.

Our results are in line with earlier reports in the literature that comorbidity is more prevalent in SUD patients with ADHD than in SUD patients without ADHD. These findings are of direct relevance for daily practice in addiction treatment centres. It shows that the subpopulation of SUD patients with ADHD, which constitutes 10–25% of treatment-seeking SUD patients, is suffering from substantially more comorbid disorders than SUD patients in general. Our finding of an ADHD prevalence of 13.9% is in line with a recent study reporting that 12% of treatment-seeking SUD patients had undiagnosed ADHD; these patients also suffered from increased impairment across several domains of daily life [27]. These findings also confirm the importance of the current trend to integrate psychiatric care and addiction treatment [28].

Strengths and limitations

This is by far the largest study to date to evaluate a SUD population for the presence of ADHD, ASPD, BPD, MD and HME using the same standardized interviews by trained professionals. Earlier studies reported either on smaller samples (e.g. Chen *et al*. reported on 465 treatment-seeking SUD patients [3]) or on comorbid problems instead of comorbid diagnoses (e.g. Chan *et al*. reported on 1956 adults and 4930 adolescents [4]). In addition, great care was taken to interpret symptoms and previous history correctly using validated instruments, which is especially important when diagnosing ADHD in SUD patients. Another strength of the study is the inclusion of different types of SUD patients (alcohol- and/or drug-dependent patients, in-patients and out-patients), men and women and patients from several countries and different socio-economic and cultural backgrounds, altogether strongly enhancing generalizability. As there were only small differences in age between the study sample and the patients who dropped out before completing the full assessment, the study sample can be regarded to be representative of the total population in the IASP study.

However, this study also has some important limitations. First, the presence of comorbid disorders was based on structured interviews (MINI-plus and SCID II) which, in this population, might be less suitable for accurate diagnostics, as some of the symptoms that are assessed may be due to the effects of drug use. Diagnostic assessments were performed preferably after initial stabilization of the SUD, but abstinence was not required. This may

have led to an overestimation of the comorbidity rates due to the presence of substance-induced symptoms, both in SUD patients with and without ADHD. We cannot rule out, however, that SUD patients with ADHD use more substances and as a consequence have higher rates of substance-induced comorbidities, which may have resulted in an overestimation of the ORs. Ongoing substance use may also have had an impact upon the validity of the ADHD diagnoses, as ADHD symptoms could be mimicked or suppressed by the use of substances. Unfortunately, we had no information on the abstinence status of the included patients at the time of the full assessment. However, the requirement of the presence of ADHD symptoms before age 7 years makes it extremely unlikely that substance-induced ADHD symptoms were misclassified as adult ADHD. Another limitation is the cross-sectional design of the study, which prevents us from making causal inferences on the associations that we found. Although ADHD starts in early childhood by definition and will theoretically have preceded most comorbid psychiatric disorders it is possible that, for example, depression causes ADHD-like inattention symptoms that may be misinterpreted as ADHD symptoms. However, the required criterion regarding the age of onset of ADHD symptoms and the careful interpretation of symptoms should have limited this confound. Furthermore, the information on the primary substance of abuse was obtained from self-report measures related to the current primary substance of abuse, and it included only current use of either alcohol or illicit drugs. This is a probably a simplification of reality, as many patients use multiple substances and no clear distinction between primary and non-primary substance of abuse can be made. It is unclear how this may have had a specific impact on the comorbidity rates. Severity of substance use may be related to treatment type with in-patients using more substances which, in turn, can have an effect on comorbidity. However, as we have no measures of severity of SUD over the participating wards, we have no measures of to what extent the latter is true in our international sample. It should be noted, however, that multilevel analyses were performed with site as level two, and most analyses were controlled for the primary substance of abuse. The random slope in the multi-level analysis allows the prevalence of the dependent variable to differ between sites; when sites differ in severity of substance dependence/abuse, and this is related to the outcome, the analysis corrects for this (comparable to correcting for age in a regression model, which also allows for a separate slope for men and women). Therefore, we think that differences in severity are at least partially controlled for in the analyses. Possible differences between study sites in terms of, for example, accessibility to services and comprehensiveness of treatment are another limitation. Moreover, within the framework of the multi-centre study, a pragmatic selection was made of which disorders were evaluated in the full assessment. Although other disorders such as anxiety disorders are also important, they were not included in this study. Finally, the analyses using ADHD subtype were based on relatively small subgroups, leading to reduced power and possibly false negative conclusions.

CONCLUSIONS

Numerous studies have reported on the role of ASPD and its precursor conduct disorder (CD) in the development of SUD and found that CD increased the risk of later SUD in

children with ADHD [29,30], although controversy remains as to the exact mechanism. Our increased levels of ASPD in the ADHD$^+$ group were in line with these findings.

The high rate of comorbidity in our patient population also raises fundamental questions on the concept of comorbidity. Milberger *et al*. showed that ADHD was not just the result of overlapping symptoms present in depression, bipolar disorder and anxiety disorders [31]. However, if the presence of comorbidity is not explained by overlapping symptoms, one could still argue whether the combination of, for example, ADHD, BPD and MD should be seen as the simultaneous presence of three distinct disorders or, rather, as the expression of a common underlying pathophysiology. Consistent with this, family studies suggest that ADHD shares familial risk factors with substance use and other comorbid disorders [32,33], although this may be different for alcohol use disorders and drug use disorders [32].

Another important issue is the interpretation of our findings regarding (hypo)manic episode. As the MINI Plus is used in a cross-sectional manner, emotional dysregulation can be interpreted falsely as (hypo)manic symptoms. This is important, as emotional dysregulation is frequently present in ADHD patients, especially in patients with combined or hyperactive/impulsive subtypes [34], and requires a completely different treatment approach than bipolar disorder, often with a positive response to stimulant medication [35].

The prominence and persistence of ADHD symptoms and subtypes has been shown to change over time, with a decrease of hyperactive/impulsive symptoms and an increase of inattentive symptoms in longitudinal studies [36]. The high proportion of adult ADHD patients with the combined subtype, and our findings of increased levels of current (hypo)mania, APD and BPD in this combined subtype, suggest that a substantial part of those with persistent hyperactive/impulsive symptoms is at increased risk for development of SUD together with additional comorbid disorders. This group, with persistent hyperactive/impulsive ADHD symptoms and increased drug use, appears to be characterized by the presence of a broad range of externalizing disorders probably representing a shared vulnerability for this type of psychopathology.

The classification system that is used currently in psychiatry has been challenged, and a more dimensional view on symptoms and clusters of symptoms has been proposed [37]. In the most recent revision of the DSM, a more dimensional view is proposed for the classification of personality disorders. In recent studies [38,39], in which Axis I and Axis II disorders were studied in a large sample of young adult twins, evidence was found for a clustering of symptoms and disorders in externalizing and internalizing spectra across Axis I and Axis II disorders, which contributes to a more coherent view on clinical disorders and personality disorders. This four-factor model has been corroborated with findings from genetic research [38], indicating that the association of disorders in our study might be due to a clustering of externalizing symptoms with a shared underlying genetic structure.

The implications of these findings for patient management and treatment are not yet fully clear. For example, if a patient suffers from SUD, ADHD, BPD and a major depression at the same time, what should be the first focus of therapy? Moreover, if all these disorders are to be seen as the result of one underlying externalizing cluster of symptoms, how should this

be treated? The discussion on the validity of our classification system is linked inevitably to the way in which we shape our treatment strategies. For example, Farchione *et al*. addressed this issue for the treatment of anxiety and mood disorders and postulated that the diversity of cognitive–behavioural therapy (CBT) treatment protocols developed for single disorders is redundant, as in reality therapists are faced with patients who have multiple comorbid conditions [40]. Heterogeneity in the expression of emotional symptoms should, in their view, be seen as a variation in the manifestation of an underlying broader syndrome, which requires a more unified approach in treating these symptoms. Mills *et al*. [41] developed an integrated treatment for SUD patients with comorbid PTSD which encompassed CBT interventions for treatment of SUD and PTSD and reported a significant decline of PTSD symptom severity. Van den Bosch *et al*. [42] developed and Verheul *et al*. [43] tested an integrated treatment for SUD patients with BPD using dialectical behaviour therapy. Van Emmerik-van Oortmerssen *et al*. [44] recently proposed an integrated treatment for SUD and ADHD. Future research should focus on the additional development of integrated treatment programmes for SUD patients with varying comorbid symptoms in the externalizing cluster. These integrated treatments could use CBT interventions to address symptoms across different disorders instead of focusing upon separate disorders. This is especially relevant, as pharmacological treatments of ADHD in SUD patients have been less effective than expected [45–49].

From a clinical perspective, it is of interest to investigate whether or not unfavourable treatment outcomes in SUD patients with ADHD are associated with particular comorbidities or clusters of disorders, in order to have better tools with which to identify the patients who are at risk for treatment dropout.

In summary, this multi-national study confirms that psychiatric comorbidity is the rule, rather than the exception, for SUD patients with ADHD. It clearly demonstrates the need for adequate diagnostic and treatment interventions for this patient population and strongly supports the further integration of addiction treatment facilities with general mental health services.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Relation between comorbid attention deficit hyperactivity disorder (ADHD), demographic characteristics and primary substance of abuse in treatment-seeking substance use disorder (SUD) patients.

Variable	ADHD$^-$ n=1037	ADHD$^+$ n=168	OR[abcd]	95% CI OR	σ^2_u (SE)[e]
Age: mean (SD)[b]	40.7 (11.3)	35.6 (9.6)	−4.9 (0.9)***	−6.7 to −3.1	6.1 (3.0)
Male (%)	73.1	75.6	1.2	0.8–1.8	0.09 (0.06)
Marital status (1028/163)[f]					
Single (%)	51.7	71.2	2.0***	1.4–2.5	0.16 (0.09)
Married/living with partner (%)	28.1	18.4	0.6*	0.4–0.9	0.02 (0.03)
Divorced (%)	20.2	10.4	0.5*	0.3–0.9	0.15 (0.10)
Housing (1002/161)[f]					
Homeless/shelter (%)	8.2	11.2	1.5	0.9–2.7	0.16 (0.13)
Living alone (%)	41.2	49.1	1.1	0.8–1.6	0.32 (0.15)
Living with others (%)	50.6	39.8	0.8	0.5–1.1	0.25 (0.11)
Employment status (1013/160)[f]					
Employed (%)	32.6	26.2	0.7	0.5–1.1	0.50 (0.22)
Unemployed (%)	38.8	43.8	1.3	0.9–1.8	0.12 (0.07)
Sick leave/disability (%)	28.6	30.0	1.1	0.7–1.6	0.76 (0.30)
Primary substance of abuse (1033/ 165)[f]					
Opioids (%)	10.4	11.5	0.8	0.5–1.4	4.79 (1.60)
Stimulants (%)	12.6	30.3	3.1***	2.0–5.1	0.98 (0.47)
Cannabis (%)	9.7	17.0	1.7	1.0–2.9	2.02 (0.97)
Other drug (%)	8.6	6.1	0.7	0.3–1.3	0.28 (0.19)
Alcohol (%)	58.8	35.2	0.4***	0.3–0.6	2.97 (1.04)

[a] For all variables except 'age' multi-level logistic regression analysis with random intercept, independent variable ADHD (yes/no), comorbid condition as dependent variable and site as level two, σ_u^2= level two variance of the intercept;

[b] for 'age' multi-level linear regression analysis with random intercept, independent variable ADHD (yes/no), age as dependent variable and site as level two, σ_u^2= level two variance of the intercept, mean difference (SE) instead of odds ratio (OR);

[c] reference category: no ADHD;

[d] * $P < 0.05$,

*** $P < 0.001$.

[e] In the logit scale, with the exception of 'age';

[f] number of patients with/without ADHD, this number can differ for specific outcome variables due to missing data.

Table 2

Relationship of attention deficit hyperactivity disorder (ADHD) and comorbid psychiatric disorders in treatment-seeking substance use disorder (SUD) patients.

Comorbid disorder (1037/168)[a]	ADHD$^-$	ADHD$^+$	OR[bcde]	95% CI	σ^2_u (SE)[f]
Current depression(%)[g]					
Primary substance alcohol (607/58)[a]	15.3	39.7	4.1***	2.1–7.8	0.63 (0.33)
Primary substance drugs (426/107)[a]	22.8	24.3	1.2	0.7–2.2	0.44 (0.28)
Current (hypo)mania (%)	4.1	14.9	4.3***	2.1–8.7	3.17 (1.58)
Antisocial personality disorder (%)	17.0	51.8	2.8***	1.8–4.2	0.40 (0.21)
Borderline personality disorder(%)[g]					
Primary substance alcohol (607/58)[a]	8.2	34.5	7.0***	3.1–15.6	1.55 (0.85)
Primary substance drugs (426/107)[a]	16.7	29.0	3.4	1.8–6.4	0.58 (0.37)

[a] Number of patients with/without ADHD;

[b] multi-level logistic regression analysis with random intercept, independent variable ADHD (yes/no), comorbid condition as dependent variable and site as level two, σ_u^2= level two variance of the intercept;

[c] presented is the odds ratio (OR) adjusted for age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs), Unadjusted ORs [95% confidence interval (CI) are: current depression/alcohol, OR = 4.4, 95% CI = 2.4–8.1, *P*< 0.001; current depression/drugs, OR = 1.4, 95% CI = 0.8–2.1; current (hypo)mania, OR = 5.3***, 95% CI = 2.8–9.9; antisocial personality disorder, OR = 4.1***, 95% CI = 3.1–6.0; borderline personality disorder/alcohol, OR = 8.5, 95% CI = 4.2–17.5, *P*< 0.001; borderline personality disorder/drugs, OR = 2.8, 95% CI = 1.7–4.9;

[d] *** *P* < 0.001;

[e] reference category no ADHD;

[f] in logit scale;

[g] because the relation with ADHD is modified by primary substance of abuse, the results are presented separately for alcohol and drug use disorder patients. Pooled relation ADHD with depression OR_{adj} = 2.1, 95% CI = 1.4–3.3, *P*< 0.001, OR_{unadj} = 2.3, 95% CI = 1.5–4.4, *P*< 0.001; pooled relation ADHD with borderline personality disorder, OR_{adj} = 4.7, 95% CI = 2.9–7.8, *P*< 0.001, OR_{unadj} = 4.9, 95% CI = 3.2–7.6, *P*< 0.001.

Table 3

Presence of comorbid disorders[a] in patients with and without attention deficit hyperactivity disorder (ADHD) in treatment-seeking substance use disorder (SUD) patients[b].

Number of comorbid conditions[a]	No comorbid disorder n (%)	One comorbid disorder n (%)	Two comorbid disorders n (%)	Three comorbid disorders[c] n (%)	Four comorbid disorders[c] n (%)
In patients without ADHD (*n*= 1037)	653 (63.0)	272 (26.2)	82 (7.9)	26 (2.5)	4 (0.4)
In patients with ADHD (*n*= 168)	42 (25.0)	68 (40.5)	39 (23.2)	10 (6.0)	9 (5.4)

[a] Apart from ADHD;

[b] multi-level ordinal logistic regression with site as level two variable and random slope. Dependent variable number of comorbid diagnoses and predictor ADHD (yes/no).

[c] To make the regression model more stable categories 3 and 4 comorbid disorders were pooled in this analysis. Odds ratio (OR) adjusted for for age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs); OR = 3.5 (2.5–4.9) $P < 0.001$ $\sigma^2_u = 0.495$ (0.212); $OR_{unadjuasted} = 4.5$ (3.2–6.3) $P < 0.001$ $\sigma^2_u = 0.399$ (0.175).

Table 4

Relation of attention deficit hyperactivity disorder (ADHD) subtype with the presence of other comorbid disorders in treatment-seeking substance use disorder (SUD) patients[a].

	Current depression		Current (hypo)mania		Antisocial PD		Borderline PD	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
ADHD inattentive subtype versus no ADHD[b]	3.04**	1.50–6.18	2.68	0.76–9.40	1.57	0.74 −3.31	5.04***	2.28–11.12
ADHD hyperactive/imp subtype versus no ADHD[b]	1.05	0.47–2.31	3.64**	1.22–10.82	2.34**	1.16–4.73	4.02***	1.82–8.88
ADHD combined subtype versus no ADHD[b]	2.64**	1.43–4.86	6.57***	2.61–16.6	4.51***	2.46–8.27	5.08***	2.61–9.89

[a]Multi-level logistic regression with site as level 2 variable and random slope. Comorbid disorder [depression/(hypo)mania/antisocial personality disorder (APD)/borderline] as dependent variable and subtype of ADHD as independent variable, with no ADHD as reference category. σ^2_u [standard error (SE)] depression 0.45 (0.24); (hypo)mania, 3.23 (1.62); APD 0.41 (0.21); borderline personality disorder 0.73 (0.35), all σ_u^2 in logit scale. All odds ratios (ORs) adjusted for age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs).

**$P < 0.01$;

***$P < 0.001$.

[b]no ADHD adulthood $n = 982$, ADHD adulthood attention deficit subtype $n = 44$, ADHD adulthood hyperactive and impulsive subtype $n = 46$ and ADHD adulthood combined subtype $n = 65$. Total $n = 1137$ due to missing values on covariates.