ADHD in treatment seeking patients with a substance use disorder
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Part 3 – The International ADHD in SUD Prevalence (IASP) study

Participated (Van de Glind et al., in press), the possibility that there were ADHD related differences that could have biased the estimates of ADHD cannot be fully discounted. In addition, requiring sustained abstinence as a criterion for inclusion might have resulted in more reliable information, but would have potentially excluded some of the more severely dependent participants, thereby leading to a possible underestimation of the prevalence of ADHD (Wilens, 2004).

The diagnostic accuracy of adult ADHD can be enhanced by obtaining additional information from parents or other individuals who knew the patient well during childhood. In this study, patients were approximately 40 years old and often came from dissolved families; hence it would be difficult if not impossible to track down parents or other key informants. When requiring attainment of collateral information to include SUD patients for this study, many would have been excluded. This decision however may have lowered (Barkley et al., 2002) the prevalence rates based on the CAADID.

Finally, we had limited data on reliability among interviewers in diverse locations (Polanczyk & Rohde, 2007). However, all sites were trained in the use of the MINI and the CAADID by the same clinical researcher (GvdG) and all interviewers at all sites were extensively trained using the same training manual for all assessment instruments.

Conclusions

Using the same definitions and diagnostic instruments in all countries and centers resulted in substantial reduction of the variability in the prevalence of adult ADHD reported in previous studies among SUD patients (2 -­‐83%) and treatment seeking SUD patients (10.0-­‐54.1%) to 5.4-­‐31.3%. The remaining variability was partly explained by primary substance of abuse and country.

Prevalence estimates for DSM-­‐5 were slightly higher than for DSM -­‐IV and all within the rates based on ADHD-­‐NOS criteria in DSM-­‐IV. Therefore, the change from DSM-­‐IV to DSM -­‐5 will hardly have any effect on the clinical practice in addiction treatment centers. However, given the generally high prevalence of adult ADHD in treatment seeking SUD patients and given the fact that efficacious pharmacologic (Faraone & Glatt, 2010) and cognitive behavioral (Safren, 2006) interventions exist for the treatment of adult ADHD and its potential impact upon the outcomes of SUD treatment, all treatment seeking SUD patients should be screened and, after confirmed diagnosis, treated for ADHD since the current literature indicates poor prognoses of SUD in treatment seeking SUD patients with ADHD (Wilens, 2004).
Abstract

Aims: To determine comorbidity patterns in treatment seeking SUD patients with and without adult ADHD with 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: 47 centers of SUD treatment in 10 countries.

Participants: 1,205 treatment seeking SUD patients.

Measurements: Structured diagnostic assessments were used for all disorders: presence of ADHD was assessed with the CAADID, presence of antisocial personality disorder (ASPD), major depression (MD), and (hypo)manic episode (HME) was assessed with the MINI Plus and the presence of borderline personality disorder (BPD) was assessed with the SCID II.

Findings: The prevalence of DSM-IV adult ADHD in this SUD sample was 13.9%. ASPD (OR=2.8, 95% 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 to ADHD- patients (p<.001). These results also indicate increased levels of BPD and MD for alcohol compared to drugs as primary substance of abuse. Comorbidity patterns differed between ADHD subtypes with increased MD in the inattentive and combined subtype (p<.01), increased HME and ASPD in the hyperactive/impulsive (p<.01) and combined subtypes (p<.001) and increased BPD in all subtypes (p<.001) compared to SUD patients without ADHD. 75% of ADHD patients had at least one additional comorbid disorder compared to 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
Substance use disorder, ADHD, comorbidity, antisocial personality disorder, borderline personality disorder, depression, bipolar disorder
Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a highly comorbid disorder in patients with substance use disorders (SUD; van Emmerik-van Oortmerssen et al., 2012; van de Glind et al., submitted). Moreover, both SUD and ADHD are associated with various other comorbid conditions. Substance use disorders 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 (Chen et al., 2011; Chan et al., 2008). ADHD is also associated with other comorbid conditions (Bernardi et al., 2012; Kessler et al., 2006). Few studies have investigated the comorbidity of patients with both ADHD and SUD, reporting consistently a higher prevalence of additional psychiatric disorders in SUD patients with ADHD (ADHD+) compared to SUD patients without ADHD (ADHD-) (Carpentier et al., 2011; Kim et al., 2006; Wilens et al., 2005; King et al., 1999). 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-occurring 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 (Arias et al., 2008) and ADHD (Castells et al., 2011). 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 sub-groups 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 (predominantly inattentive, predominately hyperactive/impulsive, combined) seem to be associated with different comorbidity patterns in adolescent (Tamm et al., 2012; Elkins et al., 2007; Sobanski et al., 2008) and adult ADHD (Larsson et al., 2011; Friedrichs et al., 2012; Wilens et al., 2009; Sprafkin et al., 2007) patients. No gender differences in comorbidity were reported in adult ADHD patients (Friedrichs et al., 2012). However, it is unknown whether 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 vs. illicit drugs) in this population. This information on comorbidity patterns in different sub-groups of SUD patients with adult ADHD is needed for the development of targeted and integrated treatment interventions, which not only focus 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 and taking into account possible differences related to gender and primary substance of abuse (alcohol vs. 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 (ICASA, 2013). In this two-stage study, a total of 3,558 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. (in press). Here we provide a short summary of the methodology.

**Participants**

In the IASP study, patients aged 18-65 years consecutively referred to participating addiction treatment centers in the period July 2009 to November 2011 were invited to participate. A total of 47 centers in 10 countries (Australia, Belgium, France, Hungary, The Netherlands, Norway, Spain, Sweden, Switzerland, and the USA) participated in the screening phase, including both
inpatient and outpatient treatment facilities serving both alcohol and/or illicit drug dependent patients. Seven of these countries (France, Hungary, 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 fill out 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 3,558 participants were included in the screening phase of the IASP study (van de Glind et al., in press). Of these, 1,276 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 1,205 patients with a complete set of assessments. The analyses in this report are based on these 1,205 patients. There were no significant differences between the study population (N=1,205) and the patients who dropped out (N=1,392) 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, \( p = .003 \)) and Spain (mean age difference 3.3 years, \( p < .001 \)). Detailed information on demographics, primary substance of abuse and recruitment setting is provided in the supplementary material (see table 1 of chapter 5, p 83 in this thesis) and can be found in Van de Glind et al., (in press).

**Design and procedure**

The IASP study was approved by the regional medical-ethical committees of all participating centers. 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 filled out 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 center within two to four weeks after the screening, and included a face-to-face diagnostic evaluation for ADHD, SUD, current and lifetime major depression, current and lifetime (hypo)mania, borderline personality disorder and antisocial personality disorder. 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 (van de Glind et al., in press). The Conners’ Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (Epstein & Kollins, 2006) was used for the diagnosis of DSM-IV ADHD. The CAADID is an extensive semi-structured interview addressing the presence of ADHD, and 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 seven), 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 better account for the presence of ADHD symptoms. Modules of the Mini International Neuropsychiatric Interview (MINI Plus) (Sheehan et al., 1998) 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) (Williams et al., 1992; First et al., 1995). All diagnostic instruments were administered by interviewers trained in the assessment instruments.

In analyzing 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. Likewise, (hypo)mania also included substance induced (hypo)mania. Data are presented here for current major depression (MD) and current (hypo)mania (HME) only.

Data analysis
Because of the 3-level sampling structure, subjects within site within country, we used 2-level multi-level analyses. Although a 3-level structure seemed warranted, goodness of fit comparisons revealed that a 3-level model did not fit the data better than a 2-level model. Goodness of fit was assessed with the Deviance Information Criterion, (DIC) (Spiegelhalter et al., 2002) based on Markov Chain Monte Carlo modeling, 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 2-level logistic regression analysis with site as level 2 variable and random slope with the exception of the differences in age which
was tested with a 2-level linear regression analysis with site as level 2 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 2-level logistic regression analysis with site as level 2 variable and random slope, comorbid disorder as dependent variable, ADHD (Y/N) 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 by ADHD and primary substance of abuse by ADHD interaction to the logistic regression model. When the regression coefficient for an interaction term was statistical 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 2-level ordinal regression model with site as level 2 variable and random slope.

For all analyses, $p < .05$ was regarded as statistically significant. To correct for multiple testing of 4 disorders, we used Bonferroni correction (by dividing the significance threshold value by the number of tests).

In the current report, we provide unweighed estimates of the prevalence rates, which may be slightly different from the weighted estimates of ADHD in the IASP-paper on ADHD prevalence (van de Glind et al., submitted).

All statistical analyses were conducted with MLwiN 2.27 (Center for Multilevel Modelling, University of Bristol, Rasbash et al, 2013).

Results

To decide whether a 2-level or a 3-level model was warranted we compared the DIC for the models used for the main analyses (table 2): for depression DIC 2-level model 1113.98, 3-level model 1113.83, for (hypo)mania DIC 2-level model 456.223, 3-level model 456.06; ASPD, DIC 2-level model 1122.49, 3-level model 1122.80 and for BPD DIC 2-level model 893.88, 3-level model 893.64. The differences were marginal, consequently we decided to use the more parsimonious 2-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 (SD 11.3) years for the ADHD-group and a significantly younger mean age of 35.6 (SD 9.6) in the
ADHD+ group. In the ADHD+ group significantly more subjects were single \((p<.001)\), less were married or living with partner \((p<.05)\), and less were divorced \((p<.05)\). Significantly more subjects in the ADHD+ group reported stimulants and cannabis as primary drug of abuse, and significantly less subjects reported alcohol as their primary substance of abuse (all \(p<.001\)).

**Comorbid disorders**
Table 2 shows that all comorbid disorders were more frequently present 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 by 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 \((OR = 3.5 (2.5 – 4.9) p < .001 \quad \sigma2u = 0.495 (0.212))\).

**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.
Table 1: Relation between comorbid ADHD, demographic characteristics and primary substance of abuse in treatment seeking SUD patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADHD- N = 1,037</th>
<th>ADHD+ N = 168</th>
<th>OR^12^</th>
<th>95% CI</th>
<th>OR</th>
<th>σ^2 (SE)^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: mean (SD)^2</td>
<td>40.7 (11.3)</td>
<td>35.6 (9.6)</td>
<td>-4.9</td>
<td>9.0</td>
<td>-6.7 - -3.1</td>
<td>6.1 (3.0)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>73.1</td>
<td>75.6</td>
<td>1.2</td>
<td></td>
<td>0.8 – 1.8</td>
<td>0.09 (0.06)</td>
</tr>
<tr>
<td>Marital status (1028/163)^6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Single (%)</td>
<td>51.7</td>
<td>71.2</td>
<td>2.0 '***'</td>
<td>1.4 – 2.5</td>
<td>0.16 (0.09)</td>
<td></td>
</tr>
<tr>
<td>- Married/living with partner (%)</td>
<td>28.1</td>
<td>18.4</td>
<td>0.6*</td>
<td>0.4 – 0.9</td>
<td>0.02 (0.03)</td>
<td></td>
</tr>
<tr>
<td>- Divorced (%)</td>
<td>20.2</td>
<td>10.4</td>
<td>0.5</td>
<td>0.3 – 0.9</td>
<td>0.15 (0.10)</td>
<td></td>
</tr>
<tr>
<td>Housing (1002/161)^6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Homeless/shelter (%)</td>
<td>8.2</td>
<td>11.2</td>
<td>1.5</td>
<td>0.9 – 2.7</td>
<td>0.16 (0.13)</td>
<td></td>
</tr>
<tr>
<td>- Living alone (%)</td>
<td>41.2</td>
<td>49.1</td>
<td>1.1</td>
<td>0.8 – 1.6</td>
<td>0.32 (0.15)</td>
<td></td>
</tr>
<tr>
<td>- Living with others (%)</td>
<td>50.6</td>
<td>39.8</td>
<td>0.8</td>
<td>0.5 – 1.1</td>
<td>0.25 (0.11)</td>
<td></td>
</tr>
<tr>
<td>Employment status (1013/160)^6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Employed (%)</td>
<td>32.6</td>
<td>26.2</td>
<td>0.7</td>
<td>0.5 – 1.1</td>
<td>0.50 (0.22)</td>
<td></td>
</tr>
<tr>
<td>- Unemployed (%)</td>
<td>38.8</td>
<td>43.8</td>
<td>1.3</td>
<td>0.9 – 1.8</td>
<td>0.12 (0.07)</td>
<td></td>
</tr>
<tr>
<td>- Sick leave/disability (%)</td>
<td>28.6</td>
<td>30.0</td>
<td>1.1</td>
<td>0.7 – 1.6</td>
<td>0.76 (0.30)</td>
<td></td>
</tr>
<tr>
<td>Primary substance of abuse (1033/165)^6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Opioids (%)</td>
<td>10.4</td>
<td>11.5</td>
<td>0.8</td>
<td>0.5 – 1.4</td>
<td>4.79 (1.60)</td>
<td></td>
</tr>
<tr>
<td>- Stimulants (%)</td>
<td>12.6</td>
<td>30.3</td>
<td>3.1 '***'</td>
<td>2.0 – 5.1</td>
<td>0.98 (0.47)</td>
<td></td>
</tr>
<tr>
<td>- Cannabis (%)</td>
<td>9.7</td>
<td>17.0</td>
<td>1.7</td>
<td>1.0 – 2.9</td>
<td>2.02 (0.97)</td>
<td></td>
</tr>
<tr>
<td>- Other drug (%)</td>
<td>8.6</td>
<td>6.1</td>
<td>0.7</td>
<td>0.3 – 1.3</td>
<td>0.28 (0.19)</td>
<td></td>
</tr>
<tr>
<td>- Alcohol (%)</td>
<td>58.8</td>
<td>35.2</td>
<td>0.4 '***'</td>
<td>0.3 – 0.6</td>
<td>2.97 (1.04)</td>
<td></td>
</tr>
</tbody>
</table>

^1^ for all variables except ‘age’ multi-level logistic regression analysis with random intercept, independent variable ADHD (Y/N), comorbid condition as dependent variable, and site as level 2, σ^2_2^ = level 2 variance of the intercept.

^2^ for ‘age’ multi-level linear regression analysis with random intercept, independent variable ADHD (Y/N), age as dependent variable, and site as level 2, σ^2_2^ = level 2 variance of the intercept, mean difference (SE) instead of OR.

^3^ reference category: no ADHD.

^4^ p<.05, ** p<.01, *** p<.001;

^5^ in the logit scale, with the exception of ‘age’;

^6^ number of patients with/without ADHD, this number can differ for specific outcome variables due to missing data.
patients suffered from increased impairment across several domains of daily functioning. The finding of an ADHD prevalence of 13.9% is in line with a recent study reporting centers. It shows that the subpopulation of SUD patients with ADHD, which these findings are of direct relevance for daily practice in addiction treatment.

Discussion

Table 2: Relationship of ADHD and comorbid psychiatric disorders in treatment seeking SUD patients

<table>
<thead>
<tr>
<th>Comorbid disorder (1,037/168)</th>
<th>ADHD-</th>
<th>ADHD+</th>
<th>OR^2,4,5</th>
<th>95% CI</th>
<th>σ_u (SE)^6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current depression (%)^7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- primary subst. alcohol (607/58)</td>
<td>15.3</td>
<td>39.7</td>
<td>4.1***</td>
<td>2.1 – 7.8</td>
<td>0.63 (0.33)</td>
</tr>
<tr>
<td>- primary subst. drugs (426/107)</td>
<td>22.8</td>
<td>24.3</td>
<td>1.2</td>
<td>0.7 – 2.2</td>
<td>0.44 (0.28)</td>
</tr>
<tr>
<td>Current (hypo)mania (%)</td>
<td>4.1</td>
<td>14.9</td>
<td>4.3***</td>
<td>2.1 – 8.7</td>
<td>3.17 (1.58)</td>
</tr>
<tr>
<td>Antisocial personality disorder (%)</td>
<td>17.0</td>
<td>51.8</td>
<td>2.8***</td>
<td>1.8 – 4.2</td>
<td>0.40 (0.21)</td>
</tr>
<tr>
<td>Borderline personality disorder (%)^7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- primary subst. alcohol (607/58)</td>
<td>8.2</td>
<td>34.5</td>
<td>7.0***</td>
<td>3.1 – 15.6</td>
<td>1.55 (0.85)</td>
</tr>
<tr>
<td>- primary subst. drugs (426/107)</td>
<td>16.7</td>
<td>29.0</td>
<td>3.4***</td>
<td>1.8 – 6.4</td>
<td>0.58 (0.37)</td>
</tr>
</tbody>
</table>

1) number of patients with/without ADHD;
2) multi-level logistic regression analysis with random intercept, independent variable ADHD (Y/N), comorbid condition as dependent variable, and site as level 2, σ_u^2 = level 2 variance of the intercept;
3) presented is the odds ratio adjusted for age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs), Unadjusted odds ratios (95% CI) are: current depression/alcohol, OR = 4.4, 95% CI 2.4 – 8.1, p < .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 < .001; borderline personality disorder/drugs, OR = 2.8, 95% CI 1.7 – 4.9;
4) ***: p<.001;
5) reference category no ADHD;
6) in logit scale;
7) 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<.001, OR_resubj = 2.3, 95% CI 1.5 – 4.4, p<.001; pooled relation ADHD with borderline personality disorder, OR_adj = 4.7, 95% CI 2.9-7.8, p<.001, OR_resubj = 4.9, 95% CI 3.2 – 7.6 p< .001.
Part 3 – The International ADHD in SUD Prevalence (IASP) study

142 (Santucci, 2012). These findings also confirm the importance of patients suffered from increased impairment across several domains of daily finding of an ADHD prevalence of 13.9% is in line with a recent study reporting substantially more comorbid disorders than SUD patients in general. Our patients, inpatients and outpatients, men and women, and patients from when diagnosing ADHD in SUD patients. Another strength of the study is the presence of ADHD, ASPD, BPD, MD, and HME using the same standardized.

This is by far the largest study to date to evaluate a SUD population for the finding cases. This study clearly shows that additional comorbid disorders are far more represented of the total population in the IASP study. Before completing the full assessment, the study sample can be regarded to be participating wards we have no measures to what extent the latter is true in psychiatric disorders, it is possible that for example depression causes ADHD – strongly enhancing generalizability. As there were only small levels of patient participation, the presence of the symptoms that are assessed may be due to the effects of drug use. However, this study also has some important limitations. First, the presence of the required criterion regarding the age of onset of ADHD symptoms before age seven makes it very unlikely that substance induced ADHD symptoms were misclassified as adult ADHD. Another limitation was the use of the same self-report instrument for both children and adults. However, the required criterion regarding the age of onset of ADHD symptoms before age seven makes it very unlikely that substance induced ADHD symptoms were misclassified as adult ADHD. Another limitation was the use of the same self-report instrument for both children and adults.

Table 3: Presence of comorbid disorders\(^1\) in patients with and without ADHD in treatment seeking SUD patients\(^2\)

<table>
<thead>
<tr>
<th>Number of comorbid conditions(^1)</th>
<th>no comorbid disorder (N (%))</th>
<th>1 comorbid disorder (N (%))</th>
<th>2 comorbid disorders (N (%))</th>
<th>3 comorbid disorders(^3) (N (%))</th>
<th>4 comorbid disorders(^3) (N (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients without ADHD (N=1,037)</td>
<td>653 (63.0)</td>
<td>272 (26.2)</td>
<td>82 (7.9)</td>
<td>26 (2.5)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>In patients with ADHD (N=168)</td>
<td>42 (25.0)</td>
<td>68 (40.5)</td>
<td>39 (23.2)</td>
<td>10 (6.0)</td>
<td>9 (5.4)</td>
</tr>
</tbody>
</table>

\(^1\) multilevel ordinal logistic regression with site as level 2 variable and random slope. Dependent variable number of comorbid diagnoses and predictor ADHD (Y/N).

\(^2\) To make the regression model more stable the categories 3 and 4 comorbid disorders were pooled in this analysis. OR adjusted for age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs) OR = 3.5 (2.5 – 4.9) \(p < .001\) \(\sigma^2 = 0.495 (0.212)\); OR \(\text{adjusted} = 4.5 (3.2 – 6.3) P < .001\) \(\sigma^2 = 0.399 (1.75)\).

Table 4: Relation of ADHD subtype with the presence of other comorbid disorders in treatment seeking SUD patients\(^1\)

<table>
<thead>
<tr>
<th>ADHD subtype vs. no ADHD(^2)</th>
<th>current depression (OR)</th>
<th>(95% CI)</th>
<th>current (hypo)mania (OR)</th>
<th>(95% CI)</th>
<th>Antisocial PD (OR)</th>
<th>(95% CI)</th>
<th>Borderline PD (OR)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD inattentive subtype vs. no ADHD(^2)</td>
<td>3.04**</td>
<td>1.50 – 6.18</td>
<td>2.68</td>
<td>0.76 – 9.40</td>
<td>1.57</td>
<td>0.74 – 3.31</td>
<td>5.04***</td>
<td>2.28 – 11.12</td>
</tr>
<tr>
<td>ADHD hyperactive/imp subtype vs. no ADHD(^2)</td>
<td>1.05</td>
<td>0.47 – 2.31</td>
<td>3.64**</td>
<td>1.22 – 10.82</td>
<td>2.34***</td>
<td>1.16 – 4.73</td>
<td>4.02***</td>
<td>1.82 – 8.88</td>
</tr>
<tr>
<td>ADHD combined subtype vs. no ADHD(^2)</td>
<td>2.64**</td>
<td>1.43 – 4.86</td>
<td>6.57***</td>
<td>2.61 – 16.6</td>
<td>4.51***</td>
<td>2.46 – 8.27</td>
<td>5.08***</td>
<td>2.61 – 9.89</td>
</tr>
</tbody>
</table>

\(^1\) multilevel logistic regression with site as level 2 variable and random slope. Comorbid disorder (depression/(hypo)mania/APD/Borderline) as dependent variable and subtype of ADHD as independent variable, with no ADHD as reference category. \(\sigma^2\) (SE) depression 0.45 (0.24); (hypo)mania, 3.23 (1.62); Antisocial personality disorder 0.41 (0.21); Borderline personality disorder 0.73 (0.35), all \(\sigma^2\) in logit scale. All odds ratios adjusted for age, gender, marital status, housing, employment status and primary substance of abuse (alcohol/drugs).

\(^2\) 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 \(n=1,137\) due to missing values on covariates.
Discussion

Main findings
This study clearly shows 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 odds ratios ranging from 2.1 for MD up to 7.0 for BPD in SUD patients with alcohol as 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 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 centers. 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 suffered from increased impairment across several domains of daily life as well (Huntley et al., 2012). These findings also confirm the importance of the current trend to integrate psychiatric care and addiction treatment (Santucci, 2012).

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 either reported on smaller samples (e.g. Chen et al reported on 465 treatment seeking SUD patients (Chen et al., 2011) or reported on comorbid problems instead of comorbid diagnoses (e.g. Chan et al reported on 1,956 adults and 4,930 adolescents; Chan et al., 2008). In addition, great care was taken to correctly interpret symptoms and previous history 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, inpatients and outpatients), 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 preferably performed 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 impact on 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 seven makes it very 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 inpatients using more substances, which in turn can have an effect on comorbidity. However, since we have no measures of severity of SUD over the participating wards we have no measures to what extent the latter is true in our international sample. It should be noticed however, that multi-level
analyses were performed with site as level 2 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 e.g. accessibility to services and comprehensiveness of treatment are another limitation. Moreover, within the framework of the multi-center study, a pragmatic selection was made which disorders were evaluated in the full assessment. Although other disorders such as anxiety disorders are important as well, 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.

Discussion
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 (Molina et al., 2007; Humphreys et al., 2011) 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 (Milberger et al., 1995). However, if the presence of comorbidity is not explained by overlapping symptoms, one could still argue whether the combination of, for example, ADHD, borderline personality disorder and major depression 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 (Biederman et al., 2008; Christiansen et al., 2008), although this may be different for alcohol use disorders and drug use disorders (Biederman et al., 2008).

Another important issue is the interpretation of our findings regarding (hypo)manic episode. As the MINI Plus is used in a cross-sectional way, emotional dysregulation can be falsely interpreted as (hypo) manic symptoms. This is important since emotional dysregulation is frequently present in ADHD patients, especially in patients with combined or hyperactive/impulsive...
subtypes (Skirrow et al., 2013), and requires a completely different treatment approach than bipolar disorder, with often a positive response to stimulant medication (Retz et al., 2012).

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 (Faraone et al., 2006). 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 currently used in psychiatry has been challenged and a more dimensional view on symptoms and clusters of symptoms has been proposed (Luyten et al., 2011). In the most recent revision of the DSM, a more dimensional view is proposed for the classification of personality disorders. In recent studies (Kendler et al., 2011; Roysamb et al., 2011) in which Axis I and 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 (Kendler et al., 2011), 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 inevitably linked to the way 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 Behavioral Therapy (CBT) treatment protocols developed for single disorders is redundant, since in reality therapists are faced with patients who have multiple comorbid conditions (Farchione et al., 2012). Heterogeneity in the expression of emotional symptoms should in their view be
seen as variation in the manifestation of an underlying broader syndrome, which requires a more unified approach in treating these symptoms. Mills et al (Mills et al., 2012) developed an integrated treatment for SUD patients with comorbid PTSD which encompassed CBT interventions for treatment of SUD and PTSD and reported significant decline of PTSD symptom severity. Van den Bosch et al. (2002) developed and Verheul et al. (2003) tested an integrated treatment for SUD patients with BPD using dialectical behaviour therapy. Van Emmerik-van Oortmerssen et al. (van Emmerik-van Oortmerssen et al., 2013) recently proposed an integrated treatment for SUD and ADHD. Future research should focus on additional development of integrated treatment programs 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 on separate disorders. This is especially relevant since pharmacological treatments of ADHD in SUD patients have been less effective than expected (Riggs et al., 2011; Konstenius et al., 2010; Levin et al., 2007; Levin et al., 2006; Carpentier et al., 2005).

From a clinical perspective, it is of interest to investigate whether unfavorable treatment outcomes in SUD patients with ADHD are associated with particular comorbidities or clusters of disorders, in order to have better tools to identify the patients that are at risk for treatment drop out.

In summary, this multinational 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 a further integration of addiction treatment facilities with general mental health services.