ADHD symptoms are common in patients in opioid maintenance treatment

Running title: ADHD symptoms and opioid maintenance treatment

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Introduction and aims: Knowledge of ADHD symptoms among patients in opioid maintenance treatment (OMT) is important for treatment optimization and yet limited. We investigated prevalence of ADHD symptoms, and factors associated with high ADHD symptom burden in a group of Norwegian OMT-patients.

Methods: We interviewed individuals entering OMT across Norway in two steps between 2012 and 2016. ADHD symptoms were measured by the Adult ADHD Self-Report Scale (ASRS) (n=175). We compared two groups of individuals who scored above or below the clinical cut-off score. Mental distress was measured with the General Symptom Index (GSI) of the Hopkin's Symptom Check-List (HSCL-25).

Results: Thirty-three percent of the OMT-patients screened positively for ADHD on the ASRS. Participants who scored above clinical cut-off were younger, reported more severe substance use and mental distress. When controlling for other significant variables in a logistic regression analysis, scoring above cut-off on the ASRS was associated with higher GSI (OR 1.61; 95% CI 1.03-2.50) and use of stimulants (OR 2.55; 1.13-5.76).

Conclusions: ADHD symptoms were common in these OMT-patients. High ADHD symptom burden was associated with higher mental distress and use of stimulants. This underlines a need of more systematic focus on ADHD in OMT to plan treatment accordingly.

Introduction

Adults with attention deficit hyperactivity disorder (ADHD) are clearly overrepresented among patients seeking treatment for substance use disorder (SUD) (1, 2), though prevalence rates vary between studies (3-5). A recent meta-analysis of 29 predominantly US studies estimated a pooled ADHD prevalence rate of 23% in mixed SUD populations (1). A rate of 14% (5%-31% between countries) was reported by the International ADHD in Substance use disorder Prevalence (IASP) study (6). This is the largest clinical study so far to evaluate ADHD and comorbid disorders in treatment seeking adults with SUD (7). These estimates are considerably higher than the 2.5-4% reported in epidemiological studies of the general population (2). Previous studies have demonstrated increased psychiatric comorbidity (8) and drug dependence complexity (5) in SUD patients who screen positively for ADHD, making treatment more challenging and less effective for both the ADHD (9) and the SUD (10).

A high number of individuals have been included in opioid maintenance treatment (OMT) over the past decades; an estimated 645 000 opioid users received substitution treatment in the European Union in 2014 (11). In Norway the number of OMT-patients is currently more than 7500, covering approximately 60% of its target group (12).

While the IASP study reported a higher prevalence of ADHD among users of illicit drugs compared to users of alcohol (6), others have found a lower prevalence among cocaine dependent individuals compared to alcohol- and opioid dependent individuals (1). Only a few studies have been conducted on ADHD symptoms and diagnosis in OMT-patients (13-16). Prevalence estimates vary and the methodological differences make comparison between studies difficult. Of recent studies on ADHD symptoms, one Italian study reported 19% of opioid dependent patients screening positively for ADHD (13), while a study from Taiwan found that 8% screened positive (16). These are both in contrast to an Australian study that reported a figure as high as 31% for users of heroin (5). Patients with opioid dependence and a high ADHD symptom load tend to report more serious addiction and more comorbid psychopathology, compared to those without ADHD related problems (5, 13-15). Such knowledge may be of special importance for OMT clinicians, considering the severity of harmful behaviors and death risk associated with long term opioid use independent of comorbid conditions (17).

Although ADHD medications have been shown efficient for improving ADHD symptoms in adults (18), evidence is less promising regarding the efficacy in individuals with SUD (19, 20), including those in OMT (21-23). National guidelines regulate treatment with central stimulants for patients in OMT in a number of countries due to concern of combining these medications with strong opioids, thus

restricting access to this treatment (22-24). Recent studies have shown positive effects of cognitive behavioral therapy (CBT) in ADHD patients without SUD (25) but this has not been sufficiently studied in patients with both conditions. However, the shared genetic profile of SUD and ADHD and their functional consequences, suggest that integrated treatment of SUD and ADHD with CBT may improve treatment outcome (26). A prerequisite to customize treatment is however accurate diagnostic information.

While full assessment of ADHD is time consuming and rarely practiced in OMT facilities, a brief ADHD screening is perhaps more feasible. The Adult ADHD Self-Report Scale (ASRS) has been found to have acceptable sensitivity and moderate specificity in a SUD sample (27) where approximately 1/3 of participants who scored above clinical cut-off on the ASRS were diagnosed with ADHD after full assessment. The ASRS could therefore represent an efficient tool in detecting ADHD symptoms among individuals in OMT at an early stage.

On this background we wanted to

1. Estimate the prevalence of ADHD symptoms in a sample of Norwegian OMT patients, using the ASRS.
2. Describe patient characteristics prior to treatment associated with high ADHD symptom burden.
3. Explore factors associated with high ADHD symptom burden.

Materials and Methods

Material

The present study is part of the larger Norwegian Cohort of OMT and other Substance Use Treatment (NorCOMT) multi-center study, the first results of which have been published elsewhere (28, 29). In this paper we study a subset of the NorCOMT cohort; patients who entered OMT and completed a satisfactory ASRS (n=175). In Norway OMT is typically administered by publicly funded health facilities on an outpatient basis following national guidelines (24). Apart from an opioid dependence diagnosis prior to treatment initiation, there are no further absolute criteria (e.g. age limit) to enter this treatment. OMT is usually considered a life-long treatment.

Interviews were conducted in two steps one year apart for each patient between 2012 and 2016 (T0 and T1). In the present study we utilized baseline data from T0, with the exception of ASRS which was only collected at T1. To enter the study at T0, there were no exclusion criteria beyond clinicians' assessment of suitability. Five hundred and seventy-nine (57%) of OMT patients were not considered for eligibility, primarily due to logistical problems in the treatment facilities (fig. 1). Of the 438 considered for eligibility, 88 (20%) declined and 45 (10%) did not meet for the interview. Twenty-two (5%) were not interviewed for other reasons with mental instability (6%) and intoxication (3%) logged as the most frequent explanations. Two hundred and eighty-three participants (65% of those eligible) were interviewed at T0 and 179 (63%) at T1; 175 with a valid ASRS.

<Insert figure 1 about here>

Methods

Trained treatment staff provided information about the study to new patients, obtained informed, written consent and conducted the interviews. We aimed at interviewing patients within six weeks after treatment initiation; however interviews completed within 12 weeks were accepted. Median time between the first and second interview was 410 days (range: 336-547 days). The aim of the study was to investigate patient characteristics prior to treatment associated with prevalence of ADHD symptoms at follow-up. The interview guide included questions pertaining to socio-demographic background (gender, age, birth country, children, educational level, living conditions and occupation). Excerpts from the Addiction Severity Index adapted for European use (EuropASI) (30), collected information on the participants' four most frequently used substances or addictive medications during the past six months prior to treatment. We organized use of substances into illicit and prescribed use and combined those being pharmacologically related.

We used Hopkin's Symptom Checklist, 25 item version (HSCL-25) to assess level of mental distress (31). HSCL-25 is a self-administered symptom inventory investigating symptoms of depression, anxiety and somatization (32). Respondents indicate if they have experienced different problems during the past week on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). We used the mean scores known as the Global Symptom Index (GSI) in the analysis. In our sample, internal consistency of the scale was $\alpha = 0.93$.

As a measure of level of dependence, we used the Severity of Dependence Scale (SDS), a validated five-item scale (33). The scale ranges from 0 to 15 (low to high), and is devised to measure dependence of specific substances, primarily for research purposes. Because our focus was not on one specific drug, we rephrased the items to reflect general dependence (e.g. "Did you think your use of substances was out of control?" instead of e.g. "Did you think your use of amphetamines was out of control?"). Responses were given on a 4-point Likert scale. In our sample, internal consistency of the scale was $\alpha = 0.68$.

Collection of ADHD symptoms was added at follow-up interviews. We used the six-item version of the Adult ADHD Self-Report Scale (ASRS), an instrument developed in collaboration with the World Health Organization (34). The ASRS has previously been found to have good sensitivity and moderate specificity in a sample of individuals with SUD. However, one study (n=114) found both sensitivity (0.74, 95% CI: 0.50-0.98) and specificity (0.54, 95% CI: 0.44-0.64) reduced for opioid users (24). In line with others we calculated ASRS scores with a cut-off score of 14 (scores added) or more for caseness, to optimize validity (35). In addition we analysed the data with an alternative sum score where a score of 3 or more on items 1-3 gave one point, or a score of 2 or more on items 4-6 gave one point. A sum score of 4 or more was considered a positive ADHD screen result (5, 13, 27). Lastly, we treated ASRS sum-score as a continuous variable and investigated whether it was related to the explanatory variables in correlation analyses.

Interviews with one missing item (n=4) on the ASRS were imputed using imputation of the mean, while interviews with more than one missing item were excluded from the analysis (n=4) To explore patient characteristics prior to treatment associated with scores below and above ASRS cut-off, we used variables from the first interview. The ASRS has previously demonstrated stable psychometric properties in a non-SUD population, indicating that patients who score above clinical cut-off point at one time will do the same next time (36). The IASP study also found the psychometric properties of the ASRS to be stable regardless of substance use status, but within a shorter time frame (14-28 days) (27).

Statistics

Pearson's Chi-Square test was applied for categorical variables and Student's T-test for continuous variables. The threshold for statistical significance was set at 5% with 95% confidence intervals (95 % CI) for all tests. Logistic regression analysis was applied to examine associations between high levels of ADHD symptoms and patient characteristics prior to treatment. For statistical analysis we used IBM SPSS 22.0.

Ethics

The study was approved by the Regional Ethics Committee for Medical Research (ref: 2012/1131/REK). Participation in the study was voluntary and it was made clear that declining participation would not affect the treatment provided.

Results

As ASRS was measured at follow-up, we investigated whether there were differences between those initially included and those who responded to the ASRS questionnaire. We found no differences in age, gender, type of treatment, substances used or injecting behavior. Overall 57 (33%) of the participants reported ADHD symptoms above clinical cut-off (14 points sum score) with no gender differences. Patients who scored above clinical cut-off were younger ($p<0.001$) and they more frequently reported use of stimulants ($p<0.001$), illicit benzodiazepines ($p=0.042$) and cannabis ($p=0.038$). The number of different substances used was higher for the participants who scored above clinical ASRS cut-off ($p<0.001$) and the same was true for the level of SDS ($p=0.019$). Participants with an ASRS score above clinical cut-off suffered from a higher GSI score, measured by HSCL-25, compared to those who scored below cut-off ($p=0.009$).

Using an alternative cut-off point of 4 (weighted scores), the number of patients who scored above cut-off point increased to 68 (39%). The same variables remained significant compared to the original cut-off point of 14. We also performed the analysis with ASRS as a continuous measure using linear regression, confirming our previous results.

All variables significantly related to the outcome variable ASRS above vs. below clinical cut-off score in the unadjusted analysis were included in the multivariate analysis, in addition to gender (table 2). These were age, use of stimulants, illicit benzodiazepines, cannabis, number of substances used, SDS and GSI. The adjusted analysis shows that only use of stimulants (OR 2.55; 95% CI 1.13-5.76) and a higher GSI on the HSCL-25 (OR 1.61; 95% CI 1.03-2.50) at intake to treatment were associated with scores above clinical cut-off point on the ASRS among the OMT-patients.

Discussion

In this study more than one third of OMT-patients screened positive for ADHD on the ASRS. These results were confirmed when using different cut-off points for the ASRS. In the final adjusted model, mental distress and use of stimulants were associated with scoring above cut-off on the ASRS.

The prevalence of ADHD symptoms in our study was higher than the results of two other recent studies on ADHD symptoms in OMT patients which reported respectively 8% and 19%, both using the ASRS (13, 16). This discrepancy could possibly contain cultural elements (6), as the Scandinavian countries traditionally have reported higher levels of ADHD symptoms compared to the southern parts of Europe (6), this could also be reflected among OMT-patients. Although the ASRS has been shown to have good sensitivity in identifying ADHD in SUD patients, the specificity is only moderate and even lower in patients with opioid dependence (27). Scoring above clinical cut-off on the ASRS should not be interpreted as having a DSM-5 or ICD-10 ADHD diagnosis before full clinical assessment is conducted. If the ratio of the IASP study were to be applied to our results, the prevalence of ADHD among the OMT patients in the present study would be comparable to the 11% prevalence of ADHD found among the subgroup of IASP participants reporting opioids as their primary substance of abuse (6). The results are also comparable to the former studies that have investigated the prevalence of ADHD in OMT patients (14, 22, 37). However, some of these studies are based on retrospective diagnosis of childhood ADHD rather than a present adult ADHD diagnosis (38). Two of the more extensive studies of adult ADHD among OMT patients did report higher prevalence rates (17% and 25%) (14, 15) than the roughly estimated prevalence rates that could be calculated from our screening results. This gap can probably be explained by methodological differences, such as ADHD assessment procedures and selection procedures. However, when we used the alternative cut-off point of a weighted score of 4, our prevalence rate of ADHD symptoms increased to 39%. This could imply our results with the cut-off point of 14 are on the conservative side.

Patients who scored above clinical cut-off were younger than the patients who reported below cut-off score. This differs from one report finding no age difference between the ADHD symptom status groups (16), but is consistent with another (5). This finding could be interpreted as age-related improvement of certain ADHD symptoms (13). However, another explanation could be that patients with an increased rate of ADHD symptoms have a more severe course of addiction with an earlier age of onset and may thus start treatment earlier (39). Higher severity of dependence scores and higher number of substances used by patients who screened above the clinical cut-off score in our study, are also consistent with previous findings that having increased rate of ADHD symptoms as well as an ADHD diagnosis are associated with more severe expressions of substance use in OMT

patients (13, 15, 16). The greater use of benzodiazepines and cannabis we find in our data could be attributed to the higher prevalence of psychiatric comorbidity, and to the more specific influence these substances might have on ADHD symptoms (15). E.g. the use of cannabis could be interpreted as a form of self-medication to manage sleeping problems (40) or as sedative after using stimulants (41). It could be that neurobiological differences, impaired executive functioning and more impulsivity contribute to increased SUD complexity in this patient group (5).

In our study frequent use of stimulants was associated with scores above clinical cut-off on the ASRS. Others have also found more use of amphetamines, among other drugs, in individuals with SUD and increased rate of ADHD symptoms (5) and among those with an ADHD diagnosis (6, 42) compared to those with SUD and no ADHD. As stimulants are considered first line pharmacotherapy for ADHD, they are often believed to represent a kind of self-medication for ADHD symptoms (5, 43). However, this finding contrasts some studies investigating ADHD in OMT patients specifically, which did not find more use of stimulants in the patients with ADHD (14, 15). These inconsistencies are also expressed in opinions regarding whether individuals with ADHD prefer different kinds of substances compared to those without ADHD, such as stimulants (44), alcohol and cannabis (45) or not (46, 47). Further, it is common for individuals in OMT to be poly-drug users (11) and this could be a reflection of the failure to identify particular drug use patterns among illicit drug users with ADHD (1, 43).

Mental distress was higher among patients who reported ADHD symptoms above cut-off on the ASRS. This is in line with the findings of recent studies of ADHD symptoms in OMT patients (13, 16) and previous research showing adult SUD patients with a comorbid ADHD diagnosis have more psychiatric comorbidities such as conduct disorder (43), depressive and anxiety disorders (15), compared to adults with only SUD (48). Also OMT patients with an increased rate of ADHD symptoms as well as an ADHD diagnosis have been found to have a lower quality of life, more comorbid SUD and higher frequency of anxiety disorders and depression compared to those without ADHD (13, 15, 16). Whether symptoms of anxiety and depression develop as a result of, or independently of the ADHD is however disputed (49).

Limitations and strengths

This study has important limitations. First, we must stress that only ADHD symptoms were screened for and a formal ADHD diagnosis was not set. A higher response rate at follow-up would have been beneficial, although one should keep in mind that it is a hard-to-reach patient population. However, we did not detect differences in patient characteristics between the participants lost to follow-up and those who were interviewed. We have low rates of item-missing data due to data collection by

trained interviewers. While all other variables were collected at baseline in this project, the ASRS scores were collected at a follow up interview only. Sixty-two percent of the original cohort contributed data at follow-up. It would have been beneficial if we had measured ADHD symptoms also at baseline to measure possible change in symptom burden.

Clinical implications

A comorbid ADHD diagnosis is associated with a range of psychosocial challenges and poorer treatment outcomes compared to individuals without ADHD (8, 50), but is often overlooked in clinical practice. Given the severe consequences of untreated ADHD and opioid dependence, both conditions should be appropriately identified, diagnosed and treated to optimize outcomes. Systematic use of a screening tool, such as the ASRS, is not very time consuming and could provide a basis for assessing the need of further diagnostic work. Effects of pharmacological treatment of ADHD in OMT patients are uncertain (21) and results of other therapeutic approaches (such as Cognitive Behavioral Therapy) remain to be investigated (51). Psychosocial interventions, e.g. educational remediation and structure, should nevertheless be considered as they might be helpful in managing everyday demands and thus enhance quality of life and functioning for individuals who carry heavy burdens.

Conclusions

This study assesses ADHD symptoms in individuals entering OMT with a validated screening tool. Thirty-three percent scored above clinical cut off on the Adult ADHD Self Report Scale. This emphasizes the need for ADHD screening in OMT which routinely should be dealt with by clinicians to enhance treatment outcomes.

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Figure 1

Table 1. Sociodemographics, substance use and scores on HSCL-25 for n = 175 patients before entering opioid maintenance treatment stratified by ASRS scores below or above cut-off point at one year follow-up.

		ASRS score 0-13 n=118 (67.4%)	ASRS score 14-24 n=57 (32.6%)	p value
Sociodemographics				
Male gender	n (%)	85 (72.0)	43 (75.4)	0.634
Age ^a	Mean (SD)	40 (9.4)	35 (8.7)	0.001
In work or education	n (%)	18 (15.7)	6 (10.7)	0.383
Substances/medications among 4 most frequently used 6 months prior to treatment				
Opioids (illicit)	n (%)	90 (76.3)	39 (68.4)	0.269
Stimulants	n (%)	51 (43.2)	42 (73.7)	<0.001
Benzodiazepines (illicit)	n (%)	49 (41.5)	33 (57.9)	0.042
Benzodiazepines (prescribed)	n (%)	31 (26.3)	13 (22.8)	0.621
Cannabis	n (%)	59 (50.0)	38 (66.7)	0.038
Alcohol	n (%)	17 (14.4)	8 (14.0)	0.947
Patterns of substance use				
Number of substances used (past 6 months) ^a	Mean (SD)	3.3 (2.2)	4.8 (3.0)	0.001
Severity of dependence (SDS) ^{a,b}	Mean (SD)	9.9 (3.2)	11.1 (2.9)	0.019
Global Symptom Index (GSI) as measured by mean HSCL-25 ^a	Mean (SD)	1.1 (0.8)	1.5 (0.9)	0.009

Pearson's Chi Square tests or one-way ANOVA tests were applied, significant results at $p < 0.05$ are in bold. ^a Continuous variables ^b The range for the Severity of Dependence Scale (SDS) is 0-15; from low to high dependence

Table 2. Unadjusted and adjusted odds ratios (OR) for n= 175 OMT patients for having an ASRS score above cut-off and 95% confidence intervals (CI) in a logistic regression analysis. The dependent variable is ASRS score above clinical cut-off point.

	Ref.	Unadjusted OR (CI)	p-value	Adjusted OR (CI)	p-value
Sociodemographics					
Male gender	Female	0.84 (0.41-1.73)	0.063	1.15 (0.50-2.69)	0.743
Age ^a		0.94 (0.91-0.98)	0.002	0.96 (0.92-1.00)	0.064
In work or education	No	0.39 (0.24-1.73)	0.386		
Substances/medications among 4 most frequently used 6 months prior to treatment					
Opioids (illicit)	No use	0.67 (0.33-1.36)	0.270		
Stimulants	No use	3.68 (1.84-7.36)	<0.001	2.55 (1.13-5.76)	0.024
Benzodiazepines (illicit)	No use	1.94 (1.02-3.68)	0.043	1.61 (0.78-3.34)	0.196
Benzodiazepines (licit)	No use	0.83 (0.40-1.74)	0.621		
Cannabis	No use	2.00 (1.04-3.86)	0.039	1.76 (0.84-3.71)	0.135
Alcohol	No use	0.97 (0.39-2.40)	0.947		
Patterns of substance use					
Number of substances used past 6 months ^a		1.28 (1.10-1.49)	<0.001	1.08 (0.92-1.26)	0.357
Severity of dependence (SDS) ^a		1.14 (1.02-1.27)	0.025	1.05 (0.93-1.20)	0.441
Global Symptom Index (GSI) as measured by HSCL-25 ^a		1.65 (1.14-2.40)	0.008	1.61 (1.03-2.50)	0.036

^c Continuous variables