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ADHD: prevalence and effect on opioid use disorder treatment outcome in a French sample of patients receiving medication for opioid use disorder—the influence of impulsivity as a mediating factor

Auxane Beslot[1], Marie Grall-Bronnec[2,3,7*], Marianne Balem[2], Benoit Schreck[2], Edouard-Jules Laforgue[2,4], Caroline Victorri-Vigneau[2,4], Morgane Guillou-Landreat[5,6], Juliette Leboucher[1], OPAL-Group, Gaëlle Challet-Bouju[1,2] and Clémence Cabelguen[1]

Abstract

Background Opioid use disorder (OUD) poses a global health challenge, and despite medications for opioid use disorder (MOUD) and psychosocial interventions, relapse remains a significant concern. Comorbid psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), are one of the major factors associated with poor OUD treatment outcome. We aimed to estimate the frequency of probable ADHD (in childhood and in adulthood) in patients with OUD; to assess the factors associated with this comorbidity; and to explore the factors that mediate the relationship between ADHD and OUD treatment outcome.

Methods We conducted an observational study using a sample of 229 patients aged 18 years and older who were diagnosed with OUD and had received MOUD for at least six months. Participants were assessed through a structured interview and self-report questionnaires. Multivariate logistic regressions and a mediation analysis were performed.

Results Almost half of the participants reported probable ADHD in childhood, and ADHD persisted into adulthood among two-thirds of the patients. The factors associated with poor OUD treatment outcome included earlier onset of OUD, lower education, and greater impulsivity. There was no direct effect of probable ADHD in childhood on OUD treatment outcome, but there was an indirect effect through negative urgency, the tendency to respond impulsively to negatively connoted emotional experiences.

Conclusions The findings suggest that ADHD symptoms, particularly impulsivity, may contribute to vulnerability in opioid use and play a crucial role in treatment outcomes for this population.

Trial registration: ClinicalTrials identifier NCT01847729.

Keywords Opioid use disorder, Medication for opioid use disorder, Attention deficit hyperactivity disorder, Impulsivity, Mediation, Outcome

*Correspondence:
Marie Grall-Bronnec
marie.bronnec@chu-nantes.fr
Full list of author information is available at the end of the article

Background

In the past several years, the prevalence of opioid addiction—including both legal and illegal opioids—has been increasing, as shown by the opioid crisis in the United States, which has led to a high mortality rate [1]. According to consensus recommendations, treatment of opioid use disorder (OUD) includes psychosocial interventions combined with the prescription of medications for opioid use disorder (MOUD). Despite the wide use of methadone and buprenorphine, the rate of relapse among patients involved in the process of quitting opioid use is nearly 70% during prolonged observation periods [2, 3], and the worsening of another addictive disorder—mainly alcohol use disorder—occurs for one-third of patients. Therefore, identifying factors associated with a poor clinical outcome of OUD is of major interest to clinicians [4], as these factors could help them screen high-risk patients and focus on risk factor management whenever possible. Psychiatric comorbidities are one of the major factors that have been shown to be associated with less favorable addiction-related outcomes [5, 6]. Thus, OUD is frequently associated with psychiatric disorders, including anxiety disorders, mood disorders, schizophrenia, personality disorders, and neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) [7].

ADHD affects approximately 4 to 5% of children and 2 to 3% of adults [8]. It was historically classified as a specific behavioral disorder in children and was mainly characterized by a symptomatology of hyperactivity; however, it is now recognized as a multidimensional and polyfactorial neurodevelopmental disorder. The main symptoms include dysregulated attention, impulsivity, lack of inhibition, and hyperactivity. The persistence and impact of ADHD have been established among adults [9, 10].

A strong association between ADHD and substance use disorder (SUD) has been shown in previous studies [11, 12]. The prognosis and severity of both disorders also appear to be related. Indeed, the co-occurrence of ADHD and addictions is frequently associated with more precocious and more severe profiles of addictions and with a greater risk of relapse [8, 13, 14]. ADHD seems to be a major risk factor for the initiation of SUD; however, it is also a modifiable risk factor, as early treatment of ADHD has been shown to be associated with a decreased risk of SUD later in life [15]. Several hypotheses have been proposed to explain the links between ADHD and addictions. Thus, both disorders may share a common genetic vulnerability [16]. The physiopathology of both disorders may also imply alterations in dopaminergic and noradrenergic neurological pathways [17, 18], and similarities in neuroimaging findings were found between patients with ADHD and patients with addiction symptoms such as craving [19]. Finally, patients may also seek to self-medicate symptoms of ADHD with substance use [20], particularly with cocaine use [21], as supported by recent clinical and neurobiological studies [22, 23]. With regard to the intricate and synergic links between ADHD and SUD, it might be important to consider them "dual disorders" [24] rather than separate comorbidities.

Addictions to nicotine, alcohol, cannabis and cocaine in patients with ADHD have been well documented [13, 14], as has addiction to gambling [25]. Conversely, few studies have been conducted on the specific association between OUD and ADHD. The authors showed a greater prevalence of ADHD in patients with OUD, reaching 33% when the AHDH screening tool was used [26–28], as did an earlier onset of the addictive disorder [29, 30], more psychiatric and addictive comorbidities [31, 32], and greater OUD severity [29, 32]. Studies that have explored the prevalence of ADHD in patients with OUD and how ADHD influences the treatment outcome of OUD are scarce [32]. Indeed, the diagnosis of ADHD seems not to be routine in patients with OUD. Several factors could explain this difference. There might be an overlap between symptoms of ADHD and symptoms of opioid intoxication or withdrawal, making it difficult to differentiate between the two. Opioid use could also lessen ADHD symptoms such as hyperactivity [33]. Moreover, clinicians might focus primarily on the immediate issues related to opioid addiction and the prescription of MOUD. Additionally, there might be confusion between ADHD and conduct disorder, which is another frequent comorbidity in patients with OUD [34].

Our work focused on the associations between ADHD and OUD in adult patients. We expected to observe a high prevalence of ADHD in patients with OUD, a more severe clinical profile in patients with comorbidities, and the influence of impulsivity on treatment outcome. Therefore, the objectives of the present study were to estimate the frequency of probable ADHD (in childhood and in adulthood) in patients with OUD; to assess the factors associated with this comorbidity; and to explore the factors that mediate the relationship between ADHD and OUD treatment outcome.

Methods

Procedure

For the present study, we extracted data from the OPAL ("**O**piates and **P**h**A**rmaco**L**ogy") study (ClinicalTrials identifier: NCT01847729), an observational, cross-sectional, multicenter study conducted in a population of patients with OUD receiving a MOUD. Ten clinical centers located in the western region of France (e.g., hospitals, outpatient facilities and prison health units) were

included to account for the heterogeneity of the patients with OUD [4, 35].

Participants

All patients in the OPAL study were aged 18 years and older, were diagnosed with OUD [36] and were receiving MOUD (methadone, buprenorphine, or buprenorphine-naloxone combination) for at least six months. This minimum treatment period was chosen to allow sufficient time for the adjustment and stabilization of the MOUD dosage. The exclusion criteria were difficulty reading or writing French and the presence of a guardianship.

A total of 263 patients were initially included in the OPAL study. For the present analysis, we excluded patients whose ADHD profile could not be determined because of missing data.

Measures

Patients were assessed through a face-to-face structured clinical interview conducted by one of the investigators and through a set of self-report questionnaires. The following data were collected:

Sociodemographic characteristics

The following data were collected via a structural clinical interview: age, sex, education level, marital and parental status, housing, social support status, occupational status and financial status.

ADHD screening

Each patient's history of ADHD in childhood and its persistence into adulthood were assessed using the Wender Utah Rating Scale-Child (WURS-C) [37, 38] and the Adult Self-Report Scale Symptom Checklist (ASRS v1.1) screener [39]. The WURS-C consists of 25 items that retrospectively assess ADHD symptoms present in childhood, with each item being scored from 0 to 4 on a Likert scale. The ASRS v1.1 is based on all 18 symptoms from the DSM-IV diagnostic criterion A for adult ADHD, and each symptom is scored on a five-point Likert scale according to frequency. The ASRS v1.1 screener includes only the 6 items that captured the highest strength of association with the clinical diagnosis of ADHD; those 6 items assess both the inattentive and hyperactive/impulsive dimensions [40]. Dichotomous scoring of the six items was proposed by Kessler et al., with a cutoff of 4 indicating the best score for detecting ADHD in adulthood [41].

Using the results of these tests, it was possible to screen for childhood ADHD (WURS-C score $\geq$ 46/100) and for ADHD likely to persist into adulthood (WURS-C score $\geq$ 46/100 and ASRS v1.1 screener score $\geq$ 4/6). This approach permitted the identification of three patient profiles based on their scores on the two ADHD rating scales. The first profile consisted of patients with no ADHD ("No ADHD"), i.e., those who did not have symptoms in childhood (WURS-C score < 46/100), regardless of the ASRS score. In accordance with the DSM diagnostic criteria, we considered that an absence of symptoms in childhood made a diagnosis in adulthood less likely [42]. The other two profiles were obtained from patients who reported probable ADHD in childhood ("probable ADHD in childhood"). The second profile included patients who were considered to have a history of probable ADHD in childhood that resolved in adulthood ("ADHD remission": WURS-C score $\geq$ 46/100 but ASRS v1.1 < 4/6). Finally, the third profile was composed of patients who were considered to have a history of probable ADHD in childhood that was still symptomatic in adulthood ("ADHD persistence") (WURS-C score $\geq$ 46/100 and ASRS v1.1 $\geq$ 4/6). We also assessed whether the patients were taking ADHD-specific medication at the time of inclusion.

Impulsivity characteristics

Impulsivity was measured using a short version of the UPPS Impulsive Behavior Scale (UPPS-P) [43, 44]. The UPPS-P is a self-administered questionnaire assessing five dimensions of impulsivity: positive urgency, negative urgency, lack of perseverance, lack of premeditation, and sensation seeking. The positive/negative urgency dimensions assess the tendency to respond impulsively to positively/negatively connoted emotional experiences. A lack of perseverance indicates the inability to persist with tasks despite boredom or fatigue. A lack of premeditation is defined by the inability to consider the consequences of an action before carrying it out. Sensation seeking refers to the tendency to seek intense sensory or emotional experiences. The short version of the UPPS-P is a 20-item version reduced from the original 45-item UPPS [44]. Each dimension is assessed by four questions rated from 1 to 4 on a Likert scale.

OUD characteristics

The data collected covered two distinct time periods: before and after the initiation of the MOUD and included age at first opioid administration, age at onset of OUD, age at first attempt to quit opioids (after withdrawal or initiation of a MOUD), current opioid use despite MOUD (i.e. self-reported use over the previous 6 months, even episodic) or opioid abstinence (i.e. full remission of the OUD), negative consequences related to OUD (financial, socioaffective, psychiatric, medical, professional, or legal), and the presence of drug users in close social circles (family members and friends). Fraudulent ways of obtaining MOUD (through "pharmacy shopping" and

"doctor shopping") were also reported. OUD treatment failure was defined by the persistence of opioid use and/or the worsening of another addictive disorder (regarding substances other than opioid or gambling practice) [4].

Statistical analysis

Continuous variables are described by their means and standard deviations, and categorical variables are described by numbers and percentages. The occasional missing data present in the self-report questionnaires (WURS-C and UPPS-P) were imputed either by the average of the items of the scale (WURS-C) or by the average of the items of the concerned dimension (UPPS-P), only when less than 50% of the items of the scale or of the dimension were missing. When this imputation was not possible due to the excessive number of missing items, the patients were excluded from the analysis.

We first divided the sample into two groups according to their ADHD status in childhood ("No ADHD" and "Probable ADHD in childhood"). Factors associated with probable ADHD in childhood were identified using two-step multivariate logistic regression. All the variables of interest were first compared between the two groups using the chi-square or Fisher test for qualitative variables and Student's or Wilcoxon test for quantitative variables. P-values were corrected for multiple testing with the Benjamini-Hochberg procedure. Only variables that were significant at a p-value of 0.20 within the corresponding bivariate logistic regressions were subsequently entered into the multivariate model, excluding those for which conditions of independence or collinearity were not verified. Finally, an optimization selection procedure (backward) was applied using the Akaike information criterion (AIC) [45]. The aim of the backward selection was to determine the set of variables that would provide the best fit for the model. At the end of the procedure, only variables that were significant at the 0.05 p-value in the model were interpretable. The corresponding odds ratio and associated 95% confidence interval were estimated.

A mediation analysis was then conducted to explain the effect of probable ADHD in childhood on the failure of OUD treatment, using the variables significantly associated with the "probable ADHD in childhood" profile as mediators. Structural equation modeling (SEM) [46] was used in the form of path analysis. First, the occurrence of a mediating effect was explored with a Satorra-Bentler scaled χ2 difference test [47], which compares a full model that includes all possible indirect paths with a model without any indirect paths. In the case of a significant result, a mediating effect was assumed to be present, and all indirect paths were tested one at a time *via* an iterative procedure, with the new model tested against the former at each iteration *via* a Satorra-Bentler scaled χ^2 difference test. The procedure was repeated until adding indirect path(s) did not improve the model fit. The fit of the final model was estimated using the root mean square error of approximation (RMSEA) and the comparative fit index (CFI), both of which were computed using Satorra-Bentler corrected χ^2 values [47]. A RMSEA < 0.05 and a CFI > 0.95 were considered to indicate a good fit [48]. The strength and direction of the association were estimated with beta coefficients, and we used completely standardized effect sizes to eliminate the various scales of the variables included in the model [49]. The 95% confidence intervals (95% CIs) of the SEM coefficients were estimated *via* the bootstrap resampling technique (100 replicates).

Finally, the same analysis approach (two-step multivariate logistic regression and mediation analysis) was applied to the subpopulation of "probable ADHD in childhood" patients, who were divided into two groups according to their adulthood ADHD profile ("ADHD remission" and "ADHD persistence").

Descriptive analyses and logistic regressions were performed with Stata SE 16.0. SEMs were fitted using a robust maximum-likelihood estimator with a Satorra-Bentler correction (MLM) [47] and the lavaan package for R software 4.0.2 [50, 51].

Ethics

The OPAL study was conducted in accordance with the Good Clinical Practice Guidelines and the Declaration of Helsinki. The study was approved by the local ethics committee. The participants were informed about this study, and their written consent was systematically collected.

Results

Description of the sample

A descriptive analysis was performed on a selected sample ($N=229$), after excluding patients with missing data ($N=34$). MOUD duration were 49.99 months (SD = 52.82) in average, with no significant difference between patients with or without ADHD ($p=0.705$).

ADHD profile

Among the 229 selected patients, nearly half reported probable ADHD in childhood ("ADHD+") ($N=105$, 46%). Among these patients, ADHD symptoms resolved for 36 ("ADHD remission") patients (34% of the "ADHD+" group) and probably persisted for 69 ("ADHD persistence") patients (66% of the "ADHD+" group). Participant selection and repartition are described in the flow chart provided in Fig. 1.

No patient was receiving specific pharmacological ADHD treatment at the time of inclusion in the study.

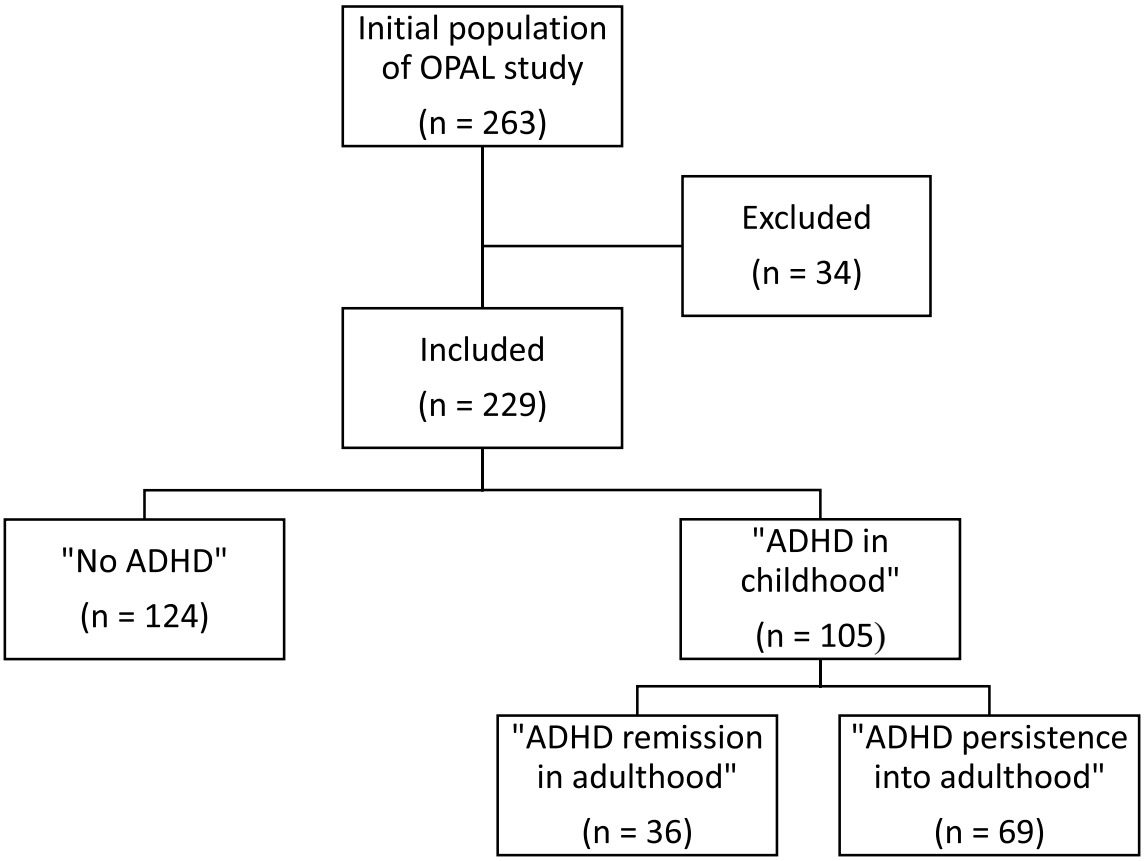

Fig. 1 Flow chart

OUD treatment outcome

OUD treatment was considered "successful" for 96 patients and "unsuccessful" for 133 patients (42% and 58%, respectively).

Factors associated with probable ADHD in childhood

Among the 25 candidate variables, 10 had a p-value ≤ 0.2 in the bivariate analysis (Table 1) and were retained for inclusion in the multivariate logistic regression. After the optimization selection procedure, we obtained the final model detailed in Table 2. Factors that were significantly associated with "ADHD+" were earlier age of onset, lower education level, higher negative urgency score, greater (lack of) premeditation score and higher sensation seeking score.

Mediation between probable ADHD in childhood and OUD outcome

The results of the iterative procedure comparing the full model, the model without any indirect path and the final model are presented in Table 3. The full model corresponds to the model with five mediating effects—education level, age at first opioid use and three UPPS scores (negative urgency, lack of premeditation and sensation seeking)—for the relationship between probable ADHD in childhood and OUD treatment failure. A significant decrease in model fit was observed between the model without any indirect paths compared to the full model, which indicated the need to search for mediating effect(s). After the iterative procedure, the final model selected displayed a very good fit (RMSEA = 0.000, CFI = 1.000). The final model that best fit the data is schematized in Fig. 2, with estimated beta coefficients indicated for each path. There was no direct effect of probable ADHD in childhood on OUD treatment failure, and only an indirect effect through negative urgency was observed, with a mediation ratio of 44% (Table 4).

Factors associated with probable ADHD persistence into adulthood

Among the 25 candidate variables, 5 had a p-value ≤ 0.2 in the bivariate analysis (Table 5) and were retained for inclusion in the multivariate logistic regression. After the optimization selection procedure, we obtained the final model detailed in Table 6. Factors that remained

Table 1 Description of the global sample and comparison between the "No ADHD" and "ADHD in childhood" groups ($n = 229$)

	Global sample $n = 229$	**"ADHD in childhood"** $n = 105$	**"No ADHD"** $n = 124$	**Adjusted** *p*-value
Sociodemographic characteristics				
Sex—women (n (%))	58 (25.33%)	26 (24.76%)	32 (25.81%)	0.890
Age (μ (σ))	34.59 (7.47)	34.37 (7.91)	34.78 (7.10)	0.755
Marital status – living alone (n (%))	144 (62.88%)	64 (60.95%)	80 (64.52%)	0.716
Social circle – close relationships (n (%))	212 (92.58%)	96 (91.43%)	116 (93.55%)	0.705
Educational level – at least high school graduate (n (%))	89 (38.86)	31 (29.52)	58 (46.77)	0.030
Professional activity – being inactive (n (%))	121 (52.84%)	61 (58.10%)	60 (48.39%)	0.327
Stable housing (n (%))	203 (88.65%)	93 (88.57%)	110 (88.71%)	0.974
OUD characteristics				
OUD duration (μ (σ))	49.99 (52.82)	52.57 (54.54)	47.80 (51.45)	0.705
OUD treatment failure (n (%))	133 (58.08%)	66 (62.86%)	67 (54.03%)	0.334
Drug-using family members or friends (n (%))	170 (74.24%)	82 (78.10%)	88 (70.97%)	0.380
Age of first opioid use (μ (σ))	20.41 (5.17)	19.30 (5.05)	21.36 (5.10)	0.009
Age of first quitting attempt (μ (σ))	25.84 (5.94)	25.05 (6.30)	26.52 (5.55)	0.179
Age of onset of OUD (μ (σ))	22.69 (5.62)	21.70 (5.75)	23.52 (5.40)	0.046
Several prescribers (n (%))	22 (9.61%)	9 (8.57%)	13 (10.48%)	0.739
Several pharmacies (n (%))	20 (8.73%)	10 (9.52%)	10 (8.06%)	0.755
OUD negative consequences				
Psychiatric problems (n (%))	161 (70.31%)	77 (73.33%)	84 (67.74%)	0.544
Somatic problems (n (%))	74 (33.31%)	39 (37.14%)	35 (28.23%)	0.327
Professional problems (n (%))	128 (55.90%)	51 (58.10%)	67 (54.03%)	0.705
Socioaffective problems (n (%))	161 (70.31%)	80 (76.19%)	81 (65.32%)	0.190
Legal problems (n (%))	113 (49.34%)	56 (53.33%)	57 (45.97%)	0.434
Financial problems (n (%))	160 (69.87%)	78 (74.29%)	82 (66.13%)	0.334
Impulsivity				
UPPS: Negative urgency [/16] (μ (σ))	10.50 (2.94)	11.42 (2.84)	9.72 (2.80)	0.001
UPPS: Positive urgency [/16] (μ (σ))	10.39 (2.59)	11.14 (2.24)	9.76 (2.70)	0.001
UPPS: Lack of premeditation [/16] (μ (σ))	8.37 (2.30)	8.97 (2.37)	7.87 (2.13)	0.002
UPPS: Lack of perseverance [/16] (μ (σ))	8.41 (2.67)	9.10 (2.74)	7.82 (2.47)	0.002
UPPS: Sensation seeking [/16] (μ (σ))	10.64 (2.94)	11.32 (2.92)	10.07 (2.85)	0.007

μ: mean; σ: standard deviation

Table 2 Factors associated with probable ADHD in childhood: multivariate analysis ($n = 229$)

	OR [$CI_{95\%}$]	***p*-value**
Educational level—at least high school graduate	0.46 [0.25 ; 0.84]	**0.011**
Age of first opioid use	0.94 [0.88 ; 0.99]	**0.034**
UPPS: Negative urgency	1.16 [1.04 ; 1.30]	**0.009**
UPPS: Lack of premeditation	1.14 [1.04 ; 1.30]	**0.015**
UPPS: Sensation seeking	1.12 [1.01 ; 1.23]	**0.045**

OR [$CI_{95\%}$]: odds ratio and associated 95% confidence interval; p-values indicated in bold are those under 0.05 (level of statistical significance)

significantly associated with "ADHD persistence" were higher lack of premeditation and lack of perseverance scores.

Table 3 Results of the iterative procedure used to obtain the final model of the mediation analysis between probable ADHD in childhood and OUD treatment failure ($n = 229$)

Model	**RMSEA**	**CFI**	**χ2 value**	**χ2 difference test**
Full model	0.000	1.000	0.000	
Model without any indirect path	0.162	0.532	27.700	+27.700 $p < 0.001$
Final model	0.000	1.000	1.826	-25.874 $p < 0.001$

CFI: comparative fit index; RMSEA: root mean square error of approximation

Mediation between probable ADHD persistence into adulthood and OUD outcome

The results of the iterative procedure comparing the full model, the model without any indirect path and the final

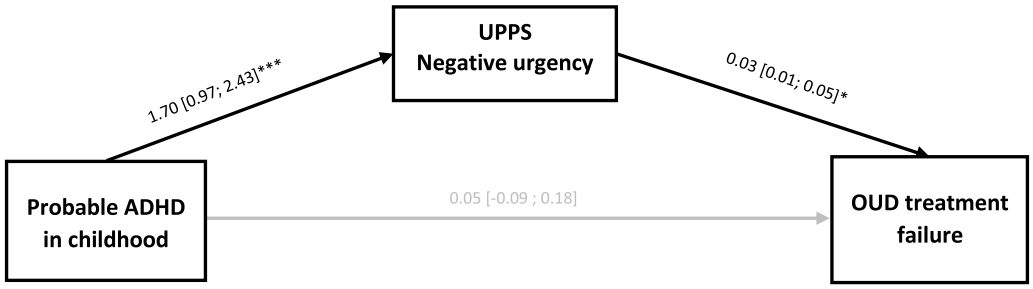

Fig. 2 Final model of mediation analysis between probable ADHD in childhood and OUD treatment failure ($n = 229$)

Table 4 Contribution of the different pathways to the explanation of OUD treatment failure ($n = 229$)

Probable ADHD in childhood → UPPS Negative urgency → OUD treatment failure	Standardized coefficient [$CI_{95\%}$]	*p*-value
Direct effect	0.05 [– 0.09; 0.18]	0.504
Indirect effect (through UPPS Negative urgency)	0.04 [0.01; 0.09]	**0.036**
Total effect	0.09 [– 0.04; 0.22]	0.176
Proportion mediated	0.44 [0.05; 0.87]	**0.041**

[$CI_{95\%}$]: 95% confidence interval; p-values indicated in bold are those under 0.05 (level of statistical significance)

model are presented in Table 7. The full model corresponds to the model with three mediating effects (UPPS negative urgency, UPPS lack of premeditation and UPPS sensation of seeking) on the relationship between probable ADHD persistence into adulthood and OUD treatment failure. The Satorra-Bentler scaled $\chi 2$ difference test between the full model including all of the indirect paths and the model without any indirect path was not significant at the 5% level ($\chi 2$ difference $= +1.258$, $p = 0.258$). This finding indicated that there was no significant difference between the models, and thus, there was no interest in adding mediating effects to the relationship between probable ADHD persistence into adulthood and OUD treatment failure.

Discussion

Main results

The purpose of this study was to estimate the prevalence of probable ADHD in childhood and persistence into adulthood in patients with OUD receiving MOUD, to assess factors associated with OUD/ADHD comorbidity, and to explore the factors that mediate the relationship between ADHD and OUD treatment outcome. Several key findings of this work should be highlighted.

First, the proportion of patients with probable ADHD in childhood was very high—46%. A high prevalence of ADHD symptoms among patients with OUD has already been found in several studies, which reported heterogeneous results ranging from 11 to 58%, with most studies reporting a prevalence of approximately 20%. The prevalence of ADHD was systematically greater among individuals with OUD than in the general population [26, 32, 52]. In our study, the presence of probable ADHD in childhood, whether it persisted into adulthood or not, was significantly associated with an earlier onset of opioid use. This result is congruent with those found in two other studies [26, 31] and, more generally, with studies showing earlier onset of SUD in patients with ADHD [12, 53, 54]. Several hypotheses have been proposed to explain these results. First, direct symptoms of ADHD, such as impulsivity and sensation seeking, might be determinant factors of vulnerability to substance experimentation. We can also hypothesize that patients self-medicate their symptoms of ADHD with the use of substances [52], for instance, sedative substances, to alleviate hyperactivity, although this has not been confirmed [55]. Frequent psychiatric comorbidities of ADHD, such as anxiety disorders or depressive disorders [56], could also increase the use of opioid substances [57]. We also found that a lower level of education was associated with probable ADHD in childhood. This association has also been found in previous studies on ADHD [58, 59]. This could result from direct symptoms of ADHD, such as inattention, which can impair learning abilities in childhood. Finally, an impulsivity profile with higher "negative urgency", "lack of premeditation", and "sensation seeking" scores also emerged as significant in patients with lifetime ADHD symptoms. Impulsivity is the clinical reflection of an inhibitory control deficit and is a core mechanism in ADHD. It is found at various levels: cognitive, emotional, and behavioral. These different expressions can be assessed by the different dimensions of the UPPS-P. A lack of premeditation is related to impairments in decision-making and engagement in risky behavior, which are clinical manifestations of an executive dysfunction involving a deficiency

Table 5 Description of the "ADHD in childhood" group and comparison between "ADHD remission" and "ADHD persistence" in adulthood groups ($n = 105$)

	"ADHD in childhood" $n = 105$	**"ADHD remission in adulthood" $n = 36$**	**"ADHD persistence in adulthood" $n = 69$**	**Adjusted *p*-value**
Sociodemographic characteristics				
Sex—women (n (%))	26 (24.76%)	9 (25.00%)	17 (24.64%)	0.967
Age (μ (σ))	34.37 (7.91)	33.44 (7.87)	34.86 (7.94)	0.405
Marital status – living alone (n (%))	64 (60.95%)	24 (66.67%)	40 (57.97%)	0.415
Social circle – close relationships (n (%))	96 (91.43%)	32 (88.89%)	64 (92.75%)	0.566
Educational level – at least high school graduate (n (%))	31 (29.52)	12 (33.33)	19 (27.54)	0.662
Professional activity – being inactive (n (%))	61 (58.10%)	20 (55.56%)	41 (59.42%)	0.719
Stable housing (n (%))	93 (88.57%)	31 (86.11%)	62 (89.86%)	0.562
OUD characteristics				
OUD treatment failure (n (%))	66 (62.86%)	20 (55.56%)	46 (66.67%)	0.315
OUD duration (μ (σ))	52.57 (54.54)	45.58 (53.89)	56.22 (54.91)	0.567
Drug-using family members or friends (n (%))	82 (78.10%)	26 (72.22%)	56 (81.16%)	0.315
Age of first opioid use (μ (σ))	19.30 (5.05)	19.92 (6.04)	18.97 (4.46)	0.386
Age of first quitting attempt (μ (σ))	25.05 (6.30)	24.92 (6.93)	25.12 (6.00)	0.937
Age of onset of OUD (μ (σ))	21.70 (5.75)	21.97 (6.05)	21.57 (5.62)	0.819
Several prescribers (n (%))	9 (8.57%)	5 (13.89%)	4 (5.80%)	0.181
Several pharmacies (n (%))	10 (9.52%)	3 (8.33%)	7 (10.14%)	0.967
OUD negative consequences				
Psychiatric problems (n (%))	77 (73.33%)	26 (72.22%)	51 (73.91%)	0.869
Somatic problems (n (%))	39 (37.14%)	15 (41.67%)	24 (34.78%)	0.503
Professional problems (n (%))	61 (58.10%)	20 (55.56%)	41 (59.42%)	0.749
Socioaffective problems (n (%))	80 (76.19%)	27 (75.00%)	53 (77.81%)	0.937
Legal problems (n (%))	56 (53.33%)	20 (55.56%)	36 (52.17%)	0.776
Financial problems (n (%))	78 (77.78%)	28 (77.78%)	50 (72.46%)	0.579
Impulsivity				
UPPS: Negative urgency [/16] (μ (σ))	11.42 (2.84)	10.09 (3.17)	12.11 (2.39)	0.001
UPPS: Positive urgency [/16] (μ (σ))	11.14 (2.24)	10.89 (2.48)	11.27 (2.11)	0.479
UPPS: Lack of premeditation [/16] (μ (σ))	8.97 (2.37)	6.94 (1.82)	10.03 (1.89)	0.001
UPPS: Lack of perseverance [/16] (μ (σ))	9.88 (2.67)	7.59 (2.28)	9.88 (2.65)	0.001
UPPS: Sensation seeking [/16] (μ (σ))	11.32 (2.92)	10.75 (3.78)	11.62 (2.32)	0.169

μ: mean; σ: standard deviation

Table 6 Factors associated with probable ADHD persistence in adulthood: multivariate analysis ($n = 105$)

	OR [$CI_{95\%}$]	***p*-value**
UPPS: Negative urgency	1.21 [0.99 ; 1.48]	0.581
UPPS: Lack of premeditation	2.33 [1.57 ; 3.45]	**< 0.001**
UPPS: Lack of perseverance	1.25 [1.01 ; 1.54]	**0.042**

OR [$CI_{95\%}$]: odds ratio and associated 95% confidence interval; p-values indicated in bold are those under 0.05 (level of statistical significance)

in the capacities of anticipation and planning [60]. Anomalies in the dopaminergic pathways in patients with ADHD, especially in the reward system, may develop and might underlie the presence of sensation

Table 7 Results of the iterative procedure used to obtain the final model of the mediation analysis between probable ADHD persistence in adulthood and OUD treatment failure ($n = 105$)

Model	**RMSEA**	**CFI**	**χ2 value**	**χ2 difference test**
Full model	0.164	0.904	0.010	
Model without any indirect path	0.000	1.000	1.258	+ 1.258 $p = 0.262$
Final model	.	.	.	.

CFI: comparative fit index; RMSEA: root mean square error of approximation

seeking [61, 62]. Another hypothesis is the frequent co-occurrence of sensory modulation dysfunction and ADHD and the link between sensory modulation and sensation seeking [63]. This could explain the vulnerability to experimental substance use, such as opioid use, as a way to seek intense sensorial and emotional experiences. The negative urgency dimension is important to emphasize because emotional dysregulation is increasingly being described as an integral component of ADHD [64]. A recent study carried out among adults newly diagnosed with ADHD concluded that emotional dysregulation is characterized by emotional instability and emotional impulsivity, which our results tend to support [65]. Furthermore, negative urgency probably plays an important role in the development of addictive disorders. This dimension of impulsivity could negatively impact an individual's ability to effectively adapt to adverse life events and lead to dysfunctional coping mechanisms such as substance use and, in turn, to the development of alcohol, tobacco or cannabis use disorders [66]. The use of sedative and anxiolytic substances such as opioids may be favored by a dysregulation of the response to stress and negative emotions. As negative urgency scores were not significantly different between patients with probable ADHD persistence and patients with ADHD remission, we can assume that this trait can remain a "scar" of childhood ADHD rather than a consequence of a symptom of current ADHD. Negative urgency was also found to be the single factor that significantly mediates the association between probable ADHD in childhood and OUD treatment failure. We can hypothesize that patients with greater negative urgency scores will show less capacity for inhibition when confronted with adversities during OUD treatment, such as withdrawal symptoms or craving, thus increasing the risk of relapse. Therefore, negative urgency can be considered a key risk factor for relapse or for switching addiction and should be closely monitored during OUD treatment in this population.

Second, the probable persistence of ADHD in adulthood was observed in two-thirds of the patients who were screened for ADHD in childhood. It is well established that ADHD persists most of the time even after childhood, and a recent study further clarified that the course of ADHD is often marked by fluctuating symptoms between childhood and young adulthood, with sustained remission in less than 10% of the cases [67]. The "lack of premeditation" and "lack of perseverance" impulsivity dimensions were the only factors we identified as associated with the persistence of probable ADHD. A lack of perseverance could be related to executive dysfunction or increased fatigability due to ADHD symptoms [68]. As previously mentioned, the lack of premeditation is linked to decision-making impairments and risk-taking behaviors [69], which are clinical correlates of executive dysfunction. In particular, inhibitory control deficits are considered a phenotype in adults with ADHD [70].

Both the precociousness of opioid use and the small differences between patients who were screened for childhood ADHD that persisted or resolved suggested that the influence of ADHD on OUD outcome occurred beginning in childhood and not *via* the direct influence of symptoms in adulthood. Many complex mechanisms are likely involved and intertwined. Impulsivity and emotional dysregulation in ADHD might lead to greater risk seeking and inefficient coping strategies when confronted with adversity. Psychiatric comorbidities of ADHD might also participate in the occurrence of addiction and response to treatment.

Finally, one important lesson from the study was the absence of specific treatment for ADHD in all patients with probable ADHD persistence into adulthood, despite the theoretical indication for treatment. It is important to note that no medication had marketing authorization in adults in France at the time of recruitment, with the exception of those already prescribed since childhood, without interruption. Although few studies have been conducted on this topic and the effectiveness of psychostimulant medication for ADHD seems unclear [71, 72], no adverse effects were found in the literature when psychostimulant treatment was used in patients with OUD or treated by MOUD when contraindications were respected. The risk of misuse of psychostimulants seems low [55]. This underprescription of psychostimulants in these patients could be related to a lack of identification of ADHD or to a lack of training or reluctance of prescribers concerning the management of the comorbidity of OUD and ADHD. It is important to specify that methylphenidate for adult patients with ADHD has only been authorized in France since 2021 [73].

Strengths and limitations of the study

These results must be viewed within the context of several limitations. The main limitation of the study is its cross-sectional nature, as we cannot establish a causal hypothesis between probable ADHD in childhood or adulthood and the associated factors. Moreover, since part of the data collection was declarative and retrospective, recall bias cannot be ruled out. Defining success or failure of OUD treatment was a tough challenge. We chose to be stringent about criteria of OUD success to ensure that we isolated truly improved patients in the "success" group. Abstaining from any opioid use thus corresponded to the definition of full remission of the disorder according to the ICD-11. However, this choice is debatable: in the context of OUD, episodic use and/or relapses are to be

expected. If transient, they do not necessarily constitute a treatment failure. We cannot exclude the possibility that some patients, treated for a long time, may have experienced multiple states (success or failure) at different times during their follow-up. Indeed, patients had been treated on average for several years, and MOUD duration constitute a potential bias when analyzing relapses, that are expected to occur more frequently. The validity of the ADHD diagnosis is a limitation frequently found in studies in this population. The scale used in the present study to assess the presence of probable ADHD in adulthood was the ASRS v1.1 screener, which is a screening scale [39]. Therefore, there is a risk of over-diagnosis among patients with symptoms suggestive of ADHD but possibly not specific enough to allow a diagnosis to be made. A diagnosis should normally be made through a structured interview such as the DIVA [74]. However, to increase the reliability of the ADHD diagnosis, the results of the WURS, which assesses ADHD in childhood, were also taken into account. Indeed, because ADHD is a neurodevelopmental disorder, we considered that a diagnosis of probable ADHD implied the presence of preexisting symptoms in childhood. Thus, we limited the risk of considering patients with attentional or hyperactivity symptoms related to causes other than ADHD, such as existing SUD or mood and anxiety comorbidities common in this population, to be ADHD [56, 75]. The combination of the WURS-C and ASRS v1.1 screener questionnaires is considered by several studies to be sufficient for reliably suggesting a diagnosis of ADHD [76]. The fact that patients had been treated and stabilized on MOUD for six months also helped to avoid confounding bias, as symptoms of inattention or hyperactivity could also be directly related to the effects of opioid intoxication or withdrawal. Another limitation is the absence of a clinical assessment of psychiatric comorbidities and associated treatments. As an association between ADHD and psychiatric comorbidities has been well demonstrated [56, 77, 78] and the presence of psychiatric disorders is associated with a greater frequency and severity of addictive disorders, there may be confounding bias regarding the characteristics of OUD and the outcome of treatment. However, psychiatric problems reported as negative consequences of OUD were not significantly different between patients with and without ADHD symptoms. These findings suggest that the prevalence of psychiatric disorders was similar. Finally, the acceptance rate to participate in the OPAL study would have been interesting to calculate. Unfortunately, the study protocol did not include recording the number of eligible patients, the number of patients refusing to participate, and the number of patients agreeing to participate at each center. Indeed, we aimed to streamline the procedure as much as possible for the investigators, who in most centers, lacked research experience and were primarily involved in clinical activities.

These limitations are compensated for by the strengths of the study. This is one of the few studies examining the relationship between ADHD and OUD, including both patients with or without probable ADHD in childhood and patients with ADHD that probably persisted into adulthood or resolved in adulthood. As mentioned earlier, this wide perspective facilitated the identification of patients with ADHD but also permitted the analysis of the impact of childhood ADHD on OUD later in life. The large number of subjects allowed for sufficient power of the statistical analyses.

Perspectives

This study is a reminder of the significant prevalence of ADHD among patients with OUD. The development of OUD seems to depend more on ADHD in childhood and its consequences than on the direct influence of ADHD in adulthood. These results reinforce the need for early and appropriate treatment in children with ADHD, especially since it has been shown that pharmacological treatment in childhood has a protective effect on addictive disorders in adulthood [79, 80].

The influence of one of the impulsivity dimensions on OUD treatment failure in patients with ADHD underscores the value of systematically screening and possibly treating this disorder and assessing the negative urgency dimension in all patients with OUD and a history of ADHD. Specific management of negative urgency through adapted psychotherapeutic care could be a way to address this issue. The place for pharmacological treatment for ADHD in managing negative urgency and, more globally, emotional dysregulation has yet to be determined. A few studies have shown positive effects of psychostimulants on cognitive impulsivity and decision-making in individuals with ADHD [81–83], although additional studies should be conducted in adults with SUD in the future. Longitudinal studies may also be conducted in the future to assess the influence of ADHD on OUD development and perpetuation and on the response to treatment, as well as the interplay with other psychiatric comorbidities.

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike Information Criterion
ASRS v1.1	Adult Self-Report Scale Symptom Checklist
CFI	Comparative Fit Index
CIs	Confidence Intervals
MLM	Maximum-Likelihood estimator with a Satorra-Bentler correction
MOUD	Medication for opioid use disorderOPAL: Opiates and PhArmacoLogy
OUD	Opioid Use Disorder
RMSEA	Root Mean Square Error of Approximation

SEM	Structural Equation Modeling
SUD	Substance Use Disorder
UPPS-P	UPPS Impulsive Behavior Scale
WURS-C	Wender Utah Rating Scale-Child

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Author contributions
AB: conceptualization, writing—original draft preparation, MGB: funding acquisition, supervision, data collection, conceptualization, writing—original draft preparation, MB: analysis, writing—original draft preparation, BS: writing—review and editing, EJL: writing—review and editing, CVV: writing—review and editing, MGL: data collection, writing—review and editing, JL: conceptualization, writing—review and editing, OPAL-Group: data collection, GCB: conceptualization, writing—original draft preparation, CC: conceptualization, writing—original draft preparation. All authors read and approved the final manuscript.

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Data availability
The datasets generated and analysed during the current study are not publicly available because data generated included sensitive data according to the French Data Protection Authority (CNIL), that could not be transferred to other researchers to guarantee participants' anonymity. But they are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The OPAL study was approved by the local ethics committee. The participants were informed about this study, and their written consent was systematically collected.

Consent for publication
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Competing interests
The authors declare no competing interests.

Author details
[1]Addiction Medicine and Psychiatry Department, Nantes Université, CHU Nantes, Nantes 44000, France. [2]Nantes Université, Univ Tours, CHU Nantes, INSERM, MethodS in Patients Centered Outcomes and HEalth ResEarch, SPHERE, Nantes 44000, France. [3]HUGOPSY Network, Rennes, France. [4]Pharmacology Department, Nantes Université, CHU Nantes, Nantes 44000, France. [5]Addiction Medicine Department, CHU Brest, Brest, France. [6]Université de Bretagne Occidentale, ERCR SPURBO, Brest, France. [7]Addiction Medicine and Psychiatry Department, Saint Jacques Hospital, 85, rue Saint Jacques, Nantes cedex 1 44093, France.

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