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Chronic exposure to cocaine is associated with persistent behavioral disturbances. A cross-sectional dimensional study in outpatients with multiple substance use disorders

Florence Vorspan^{1,2,3}  · Pauline de Witt^{3,4} · El-hadi Zerdazi^{3,5} · Emily Karsinti^{1,3,6} · Kamilia Ksouda⁷ · Romain Icick^{1,3} · Frank Bellivier^{1,2,3} · Nicolas Marie^{8,9} · Georges Brousse¹⁰ · Vanessa Bloch^{3,11,12}

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Abstract

Rationale Behavioral disturbances (BD) are prevalent in patients with substance use disorders (SUD).

Objectives To test the hypothesis that chronic exposure to cocaine could favor the acquisition of BD that were not present in childhood.

Methods We used child and adult ADHD self-report screening scales (WURS-25 and ASRS-6, respectively, with their usual threshold) as assessment tools for significant BD. In a cross-sectional assessment of 382 patients with multiple SUD, we investigated BD and then “de novo” BD (i.e., by restricting the sample to patients below the threshold for childhood BD) ($N = 214$). We also tested for a gradient effect between patients’ lifetime DSM IV cocaine and opioid dependence status and the prevalence of BD.

Results BD were found in 188/382 (42.9%) subjects and in 74/214 (34.6%) subjects. Three clinical factors were associated with BD in the whole sample: the number of cocaine dependence criteria (OR = 1.36 [1.14–1.64], $p = 0.001$), the number of opioid dependence criteria (OR = 0.69 [0.52–0.91], $p = 0.010$), and a personal history of using cocaine through rapid routes of administration (OR = 0.41 [0.19–0.88], $p = 0.022$). The same three factors were associated with “de novo” BD in the restricted sample: OR = 1.35 ([1.11–1.63], $p = 0.002$), OR = 0.83 ([0.70–0.99], $p = 0.046$), and OR 0.37 ([0.16–0.86], $p = 0.022$), respectively. There were significant gradients for BD according to the cocaine exposure categories in the whole (Mantel-Haenszel, $p < 0.001$) and in the restricted sample (Mantel-Haenszel, $p = 0.002$).

Conclusions Cocaine exposure was positively associated with behavioral disturbances in a dose-dependent manner in this clinical sample, whilst opioid exposure showed a negative association.

Keywords ADHD · Screening · Scales · Behavioral sensitization · Human · Cocaine · Opioids

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Introduction

Cocaine use is still growing in Europe, with 18 million (5.4%) people reporting lifetime use and 4 million (1.2%) reporting last year use. With cocaine use, cocaine use disorder and cocaine-related mortality and morbidity are also increasing, along with cocaine-related health costs (EMCDDA 2019). Cocaine is the most commonly reported drug by patients visiting the emergency departments in 18 European countries (idem). Agitation and behavioral disturbances are the second motive, after anxiety but before chest pain, for cocaine users to visit general emergency departments (Miró et al. 2019). Although they are usually regarded as transient, going along the dopaminergic effect of the drug, there are multiple reports of persistent behavioral disturbances (BD) in patients with cocaine use disorder (Cornish and O'Brien 1996). BD are reported under different terms and conceptual contents, including high impulsivity, antisocial personality disorder, or adult attention deficit-hyperactivity disorder (ADHD).

When assessing the cocaine-related BD with the conceptual framework of ADHD, most studies show evidence for a self-treatment hypothesis. The prevalence of childhood ADHD in adult cocaine abusers seeking treatment is difficult to ascertain and ranges between 10 and 35%, dependent upon the stringency of the assessment tools (Dakwar et al. 2012; Daigre et al. 2013). Other work shows 11% of cocaine patients to have ADHD symptoms only as adults (Dakwar et al. 2012). Among adult patients with opioid dependence or under methadone maintenance treatment, the prevalence of childhood ADHD is approximately 20% (Peles et al. 2012; Evren et al. 2018).

In contrast to such data showing childhood ADHD to be a risk factor for the development of later SUD, the current study investigates as to whether chronic cocaine exposure induces *de novo* persistent behavioral disturbances in adults, particularly symptoms that resemble ADHD symptomatology, in SUD patients who did not display such significant behavioral disturbances as children.

Ideally, a prospective study would better satisfy the Bradford Hill criteria for causality, vs a cross-sectional study (Hill 1965). However, such a large prospective comparative study starting from childhood is not feasible, leaving the issue of such emergent adult behavioral disturbances uninvestigated. Although such “gold-standard” causal modeling is not feasible, data do exist to suggest the emergence of an acquired toxic behavioral syndrome in preclinical studies, suggestive of biologically-driven emergence. The exposure to rodents of repetitive intermittent cocaine or other psychostimulants induces a psychomotor sensitization (Kalivas et al. 1992) that parallels the chronic hyperlocomotion, impulsivity, and lack of concentration observed in patients with ADHD.

The present study utilizes a pre-existing database from a transversal study of adult patients in daily treatment practice of patients with SUD in order to investigate the impact of cocaine exposure on a reported *de novo* adult behavioral syndrome, and thereby on the temporal relationship and the biological gradient or dose-effect relationship of cocaine use and such an emergent behavioral syndrome.

Methods

Design This study is a secondary analysis of two studies that recruited patients with multiple SUD in the same clinical settings. The first study, METHADOSE (OSTO07013, NTC00894452) aimed at describing factors associated with requiring higher methadone oral dosage to achieve a therapeutic response in heroin-dependent patients ($N = 216$, recruited in 2008–2012). The second study, PSYCHOCOKE (AOM10165, NTC01569347), aimed at describing factors associated with cocaine-induced psychotic symptoms ($N = 419$, recruited in 2012–2016). Outpatients from several anonymous and free care centers belonging to a research network in France participated in these studies.

Assessments In both studies, patients were interviewed once, using the same retrospective structured interview that collected their whole-life substance use history, including age of onset of all substances use and lifetime DSM IV criteria of all substance dependences or abuse. As part of this protocol, patients completed the validated French versions of self-report ADHD screening tools. The Adult Self-Report Scale (ASRS) comprises 6 items and is validated to screen for adult ADHD (Caci et al. 2010; van de Glind et al. 2013), whilst the Wender Utah rating scale (WURS) comprises 25-items (Ward et al. 1993; Baylé et al. 2003; Romo et al. 2010) and is validated to screen for childhood ADHD.

Here we chose to use those screening scales as a measure of child and adult behavioral disturbance (BD). The combination of the WURS and ASRS, together with a lifetime history of substance use, provides information on the temporal emergence of behavioral symptoms following SUD. The validated thresholds of these measures for ADHD were maintained as indicants of significant behavioral disturbances.

No structured interview was used to ascertain the DSM IV childhood or adult ADHD diagnosis, and therefore, there is no validated ADHD diagnosis in this study. Patients who did not complete the self-report questionnaires were not considered for this secondary analysis.

Statistical analysis Patients' characteristics are described with mean (\pm SD) or number (%) as appropriate. Differences between patients who did and did not complete the self-report questionnaires were tested. Univariate analysis and logistic regressions were used to identify clinical factors associated with (i) significant behavioral disturbances (BD), defined as a positive screening for adult ADHD (i.e., ASRS+ *versus* ASRS-) ($N = 382$); (ii) significant "de novo" behavioral disturbances, defined as positive screening for adult ADHD in patients who were below the usual threshold for childhood ADHD (i.e., ASRS+WURS- *versus* ASRS-WURS-) ($N = 214$). Means were compared with one-way ANOVA and percentages with the chi-squared test. The logistic regression used stepwise descending methods with a level for entry of $p < 0.05$. Our hypothesis was that patients screened as having significant "de novo" behavioral disturbances would endorse more frequently clinical factors of heavy cocaine exposure, although we also wanted to observe factors associated with ASRS+ in all subjects.

Furthermore, patients were divided into four groups according to their lifetime DSM IV dependence status for cocaine and opioids, and they were investigated for biological gradient criteria. Those four groups were as follows: lifetime opioid dependence only, use or abuse but neither opioid nor cocaine dependence criteria, both lifetime opioid and cocaine dependence, and lifetime cocaine dependence only. These groups therefore provide a gradient of lifetime cocaine exposure. Rather than a classical chi-squared test to compare the prevalence of (i) significant BD (ASRS+ *versus* ASRS-) and (ii) significant "de novo" BD (ASRS+WURS- *versus* ASRS-WURS-), in our sample according to this gradient, a Mantel-Haenszel tendency test was used. This allowed testing as to whether the frequency of significant BD and significant "de novo" BD was higher in patients with a higher lifetime cocaine exposure. Lastly, as an exploratory analysis, and although this questionnaire is not primarily intended to be used as a continuous score, we also compared the mean score of the ASRS 6-item scale among those four groups with a Jonckheere-Terpstra tendency test. Statistical analysis was performed with SPSS 21.0 (IBM). All analyses were regarded as significant when $p < 0.05$.

Ethics Both studies were conducted according to French laws on bioethics. Patients were required to be free of unstable psychiatric conditions and to give a free and informed written consent. Both studies were approved by local ethics committees (CPP IDF VI and CPP IDF IV respectively). Furthermore, as the merging of the two samples was not described in the original protocols, secondary analyses were authorized after a specific ethics committee authorization (CEEI IRB00003888) in 2015.

Results

Description of the whole sample

The overall sample comprised 628 patients. The number of patients from the two studies with clinical data including ADHD screening scales was 382, being mostly males (76.2%), with a mean age of 38 (± 9) years old at the time of the interview. They all had a personal history of several SUD, with cocaine being the most frequent psychostimulant and heroin the most frequent opioid for which treatment was sought.

Completers and non-completers were not different in terms of age (38 ± 9 vs 39.9 ± 9 , ANOVA 1df $F = 3$, $p = 0.08$), age at onset of cocaine use (23.4 ± 7 vs 23.5 ± 7 , ANOVA 1df $F = 0.013$, $p = 0.90$), age at first heroin maintenance treatment (30.8 ± 7.6 vs 30.7 ± 8 , ANOVA 1df $F = 0.030$, $p = 0.86$), and sex (male 76.2% vs 75.5%, chi-square 1df = 0.84, $p = 0.45$). But patients who did answer to the self-rated questionnaires were significantly more severe in terms of the prevalence of lifetime DSM IV cocaine dependence (78.5% vs 70%, chi-square 1df = 0.019, $p = 0.012$) and of lifetime prescription of opioid maintenance treatment (43.7% vs 33.3%, chi-square 1df = 0.23, $p = 0.014$).

The characteristics of the 382 patients with available clinical data are described in Table 1. Of note, only two patients were currently under prescribed methylphenidate off-label medication, as there is no approval in France for any pharmacological treatment for adult ADHD.

The prevalence of significant behavioral disturbances observed with ADHD screening questionnaires as a tool, as defined by a score above the threshold of the ASRS scale, was 188, representing 49.2% of the sample ($N = 382$).

The number of subjects who described significant childhood BD as defined by a WURS score above 46 points was 168, representing 44% of the sample. Overall, the WURS mean score was 41.9 (± 19.8), 0–90 points among the 382 study participants. When restricting the analysis to those patients who did not qualify for significant childhood BD, defined as a WURS score below the threshold ($N = 214$), 74 participants were identified with a positive ASRS screening. These patients were then identified as having significant "de novo" BD and represented 34.6% of this subsample.

Association with significant behavioral disturbances

The results of the logistic regressions to identify clinical factors associated with (i) significant BD (ASRS+ *versus* ASRS-) and (ii) significant "de novo" BD (ASRS+WURS- *versus* ASRS-WURS-) are presented in Table 2.

The logistic regression to predict significant BD defined by positive ASRS screening in our sample was performed on 369 complete observations. The variables included in the model

Table 1 Patients characteristics ($N = 382$)

Socio-demographic variables	Mean (\pm SD) [min–max] or N (%)	N
Age (years)	38.8(\pm 9) [19–65]	382
Gender (male)	291 (76.2)	382
Education level (high school or more)	282 (73)	382
Ever been homeless	120 (31.4)	382
Ever been married	88 (23)	382
Substance use variables	Mean (SD) [min–max] or N (%)	N
Ever used opioids	283 (74.1)	382
Age of first opioid use (years)	21.6(\pm 6) [10–45]	280
Lifetime opioid dependence	226 (59.2)	382
Number of opioid dependence criteria [1–7]	4.8(\pm 2.3) [0–7]	267
Age of first OMT prescription (years)	31(\pm 7) [16–49]	213
Lifetime maximum methadone dosage (mg)	97.6(\pm 50) [20–320]	175
Ever used opioids intravenously	136 (50.6)	269
Ever used cocaine	379 (99.2)	382
Age of first cocaine use (years)	23.5 (\pm 7) [11–53]	378
Lifetime cocaine dependence	299 (78.5)	381
Number of cocaine dependence criteria [1–7]	4.5(\pm 2) [0–7]	372
Ever used cocaine daily	212 (56.7)	374
Ever used cocaine intravenously/smoked	158 (47.7)	331
Currently under prescribed off-label methylphenidate	2 (0.05)	382

were 8 that were associated with positive ASRS screening in the univariate analysis with a threshold for an entry set at $p = 0.05$. Thus, age, age at first cocaine use, age at first opioid maintenance treatment (OMT), the number of opioid dependence criteria, the number of cocaine dependence criteria, lifetime opioid dependence (OD), lifetime cocaine dependence (CD), and the use of rapid route of administration for cocaine use were entered in the stepwise descending model.

There were 3 variables retained in the model. Those variables were the number of cocaine dependence criteria (risk factor, OR = 1.369 [1.143–1.640], $p = 0.001$), two factors associated with a lower risk, namely the number of opiate dependence criteria (OR = 0.692 [0.523–0.915], $p = 0.010$), and rapid route of administration for cocaine (OR = 0.418 [0.198–0.880], $p = 0.022$). Overall, the model was significant, chi-square 26.878 (4 df) $p < 0.001$, with a Nagelkerke's $R^2 = 0.193$. The model could correctly classify 65.9% of the subjects (73.2% of unaffected subjects and 56.6% of those with significant BD).

Association with significant “de novo” behavioral disturbances

A second logistic regression was applied to describe the characteristic of ASRS+WURS- versus ASRS-WURS- subjects, the most suggestive of a temporal relationship between cocaine exposure and later significant BD acquisition. The model was built on 210 complete observations (Table 2, right columns). The same three retained variables in the model were the number of cocaine dependence criteria (OR = 1.351 [1.114–1.639], $p = 0.002$), the number of opioid dependence

criteria (OR = 0.835 [0.700–0.997], $p = 0.046$), and the use of rapid route of administration for cocaine (OR = 0.375 [0.162–0.866], $p = 0.022$). The model was also significant (chi-squared = 20.419, $p < 0.001$ with a Nagelkerke's $R^2 = 0.191$). It could correctly classify 72.3% of the subjects, 92.9% of the unaffected, and 25.6% of the subjects with significant “de novo” BD.

Biological gradient

The comparison of the prevalence of significant BD according to the lifetime dependence status toward cocaine and opioids showed a significant gradient for both the prevalence of significant BD (ASRS+) (Mantel-Haenszel tendency test = 15.620; $p < 0.001$) ($N = 365$) and for “de novo” BD (ASRS+WURS-) (Mantel-Haenszel tendency test = 9.336; $p = 0.002$) ($N = 210$) (see Fig. 1a). Lastly, when we used the mean ASRS 6-item score as a continuous variable (0–6), a significant gradient effect was observed between the four categories of cocaine exposure, in both the whole sample ($N = 365$) (Jonckheere-Terpstra tendency test = 5.406; $p < 0.001$), and in the subsample of subjects who screened negative for childhood BD ($N = 210$) (Jonckheere-Terpstra tendency test = 3.697; $p < 0.001$) (see Fig. 1b).

Discussion

In this cross-sectional study of adult patients in daily treatment practice, presenting with multiple SUDs, several results support the emergence of a toxic/acquired BD syndrome that

Table 2 Univariate analysis and logistic regressions: factors associated with significant behavioral disturbances assessed with the ASRS 6-item scale

Behavioral disturbances (Y/N)	Whole sample Univariate analysis (N = 369) Logistic regression (N = 365)		Sample restricted to subjects without significant childhood behavioral disturbances (WURS-) (univariate analysis N = 214, logistic regression N = 210)	
	Mean (SD)/N (%)	Univariate test ANOVA/Chi ² <i>p</i> Logistic regression OR [95%CI] <i>p</i>	Mean (SD)/N (%)	Univariate test ANOVA/Chi ² <i>p</i> Logistic regression OR [95%CI] <i>p</i>
Age (years)	Y 37.8 ± 8.6 N 40 ± 9	<i>F</i> = 5.664 <i>p</i> = 0.018	Y 38.9 ± 8.1 N 40.9 ± 8.4	<i>F</i> = 2.592 <i>p</i> = 0.109
Gender (male)	Y 141(78.8) N 143(75.3)	Chi ² = 0.640 <i>p</i> = 0.459	Y 57(79.2) N 105(75.5)	Chi ² = 0.350 <i>p</i> = 0.554
Ever used opioids	Y 126(70.4) N 148(77.9)	Chi ² = 2.715 <i>p</i> = 0.099	Y 50(69.4) N 112(80.6)	Chi ² = 3.296 <i>p</i> = 0.069
Age of first opioid use (years)	Y 21.2 ± 6 N 21.9 ± 5.9	<i>F</i> = 0.990 <i>p</i> = 0.321	Y 22.4 ± 6.7 N 21.6 ± 5.7	<i>F</i> = 0.510 <i>p</i> = 0.476
Lifetime opioid dependence	Y 96 (54.2) N 124 (65.6)	Chi ² = 4.929 <i>p</i> = 0.026	Y 41 (56.9) N 97 (70.3)	Chi ² = 3.740 <i>p</i> = 0.053
Number of opioid dependence criteria [1-7]	Y 4.5 ± 2.5 N 5.1 ± 2.2	<i>F</i> = 4.160 <i>p</i> = 0.042 OR 0.692 [0.523–0.915] <i>p</i> = 0.010	Y 4.5 ± 2.4 N 5.3 ± 1.9	<i>F</i> = 4.882 <i>p</i> = 0.030 OR 0.835 [0.700–0.997] <i>p</i> = 0.046
Age of first OMT prescription (years)	Y 29.9 ± 7.1 N 32 ± 7.6	<i>F</i> = 4.437 <i>p</i> = 0.036	Y 31.1 ± 7.9 N 32.5 ± 7.8	<i>F</i> = 0.802 <i>p</i> = 0.372
Lifetime maximum methadone dosage (mg)	Y 97.9 ± 40.6 N 97.2 ± 55.9	<i>F</i> = 0.009 <i>p</i> = 0.926	Y 100.5 ± 39.8 N 92.9 ± 54.9	<i>F</i> = 0.465 <i>p</i> = 0.497
Ever use opioids intravenously	Y 64 (51.6) N 72 (49.7)	Chi ² = 0.102 <i>p</i> = 0.749	Y 23 (46.9) N 55 (50)	Chi ² = 0.127 <i>p</i> = 0.721
Ever used cocaine	Y 179 (100) N 187 (98.4)	Chi ² = 2.849 <i>p</i> = 0.091	Y 72 (100) N 137 (98.6)	Chi ² = 1.046 <i>p</i> = 0.306
Age of first cocaine use (years)	Y 22.8 ± 6.6 N 24.3 ± 7.4	<i>F</i> = 3.949 <i>p</i> = 0.048	Y 24.5 ± 7.5 N 24.9 ± 7.3	<i>F</i> = 0.092 <i>p</i> = 0.762
Lifetime cocaine dependence	Y 156 (87.6) N 133 (70)	Chi ² = 16.964 <i>p</i> < 0.001	Y 60 (83.3) N 93 (66.9)	Chi ² = 6.421 <i>p</i> = 0.011
Number of cocaine dependence criteria [1-7]	Y 4.9 ± 1.8 N 3.9 ± 2.3	<i>F</i> = 22.998 <i>p</i> < 0.001 OR 1.369 [1.143–1.640] <i>p</i> = 0.001	Y 4.8 ± 1.8 N 3.7 ± 2.3	<i>F</i> = 11.954 <i>p</i> = 0.001 OR 1.351 [1.114–1.639] <i>p</i> = 0.002
Ever used cocaine daily	Y 108 (60.3) N 96 (52.7)	Chi ² = 2.114 <i>p</i> = 0.146	Y 35 (48.6) N 65 (48.9)	Chi ² = 0.001 <i>p</i> = 0.972
Ever used cocaine intravenously /smoked	Y 62 (38.5) N 96 (56.5)	Chi ² = 10.692 <i>p</i> = 0.001 OR = 0.418 [0.198–0.880] <i>p</i> = 0.022	Y 26 (40.6) N 77 (61.1)	Chi ² = 7.176 <i>p</i> = 0.007 OR = 0.375 [0.162–0.866] <i>p</i> = 0.022

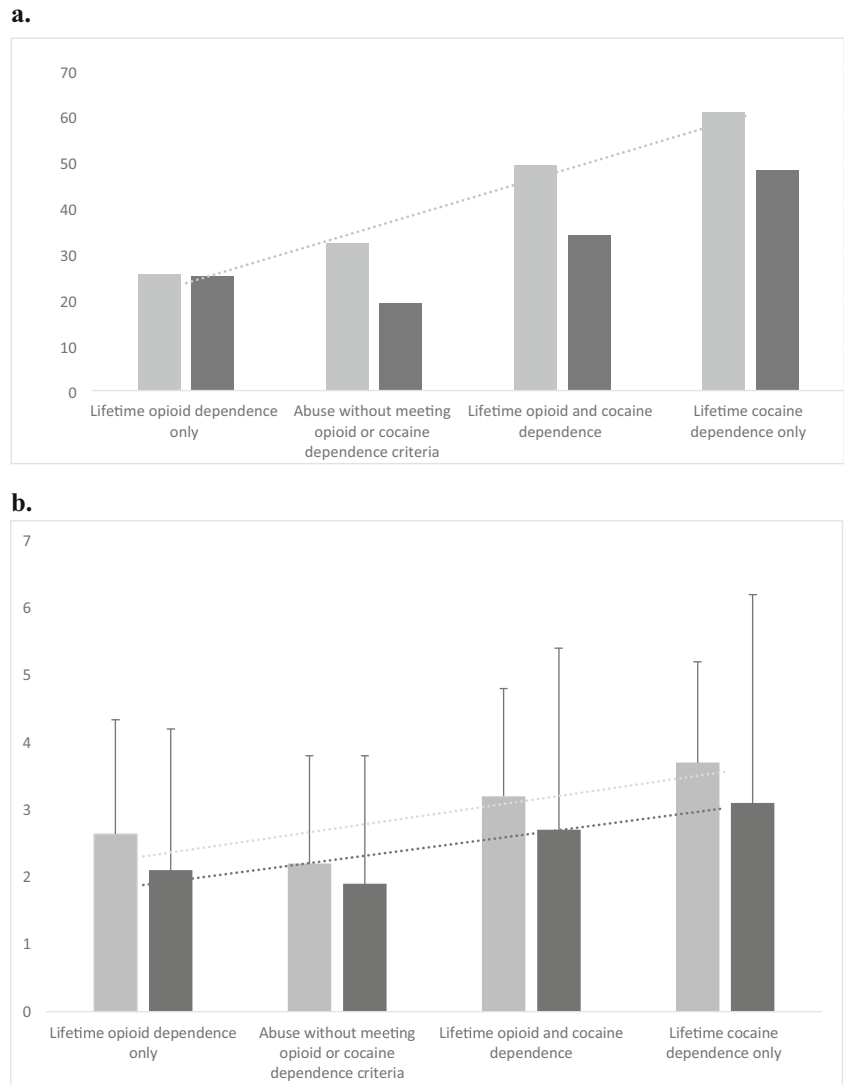
Italics: significant results (p<0.05)

ASRS, Adult Self-Report Scale; WURS, Wender Utah Rating Scale; Y, positive screening; N, no positive screening; N (SD). number (standard deviation); OR [95 CI], odds ratio with 95% confidence interval

resembles ADHD, and which associates with cocaine exposure. Indeed, the Bradford Hill criteria of time relationship were supported by data showing that 34.6% of the subsample of patients who did not qualify for significant childhood BD displayed adult significant BD. This is considerably higher

than the estimated 4.4 % satisfying criteria for adult ADHD in the general population (Fayyad et al. 2007) and also higher than the prevalence of ascertained ADHD in clinical samples of patients with SUD which is rather 10% than 35%, when stringent assessment tools are used (Dakwar et al. 2012;

Fig. 1 Gradient of significant behavioral disturbances according to cocaine exposure. **a** Percentage of ASRS+ subjects. Grey bars in the whole sample ($N = 365$) (Mantel-Haenszel tendency test = 15.620; $p < 0.001$), black bars significant “de novo” behavioral disturbances in the subsample of **WURS** - subjects ($N = 210$) (Mantel-Haenszel tendency test = 9.336; $p = 0.002$). **b** Mean (+ standard deviation) ASRS 6-item score as a continuous variable (0–6). Grey bars in the whole sample ($N = 365$) (Jonckheere-Terpstra tendency test = 5.406; $p < 0.001$), black bars in the subsample of **WURS** - subjects ($N = 210$) (Jonckheere-Terpstra tendency test = 3.697; $p < 0.001$)



Daigre et al. 2013). Assuming that patients understood the instructions to complete the WURS questionnaire in reference to childhood behaviors and ASRS in respect to their present behavior as adults, coupled to a mean age at onset of cocaine use of 23 years old, there is a clear association of chronic cocaine use and the later onset of behavioral symptoms.

The biological gradient linking the amount of cocaine exposure and the occurrence of significant “de novo” BD is supported by two results. First, a marker of cocaine exposure (the number of cocaine dependency criteria) was identified as a relevant risk factor for significant “de novo” behavioral disturbances. Second, higher cocaine exposure correlated with a higher prevalence of BD, with tendency tests regarding both this screening and the continuous ASRS score, confirming our hypothesis of a significant dose-effect relationship.

Unexpectedly, opioid use disorders, especially the number of opioid dependency criteria, were associated with a lower occurrence of significant BD. The tendency scores for both

positive screening and ASRS score as a continuum also seem to support the idea that chronic opioid dependence acts to suppress the occurrence of significant “de novo” BD in patients with multiple SUD. In previous clinical studies, the prevalence of ADHD in patients with OUD (around 20%) (Peles et al. 2012; Evren et al. 2018) is not dissimilar to the prevalence observed in CUD patients (10–35%) (Dakwar et al. 2012; Daigre et al. 2013). However, there is no direct comparison in previous human studies. Preclinical studies show behavioral sensitization to opiates is readily observed, although with effects that are less robust than the behavioral sensitization induced by stimulants, which is observed as a class effect for all stimulants. Indeed, whereas behavioral sensitization is observed with morphine and methadone, no behavioral sensitization is measured with buprenorphine (Cordonnier et al. 2007; Le Marec et al. 2011; Allouche et al. 2013). In our clinical sample, all patients were recruited during daily treatment practice. It is of note that among the

226 patients with a lifetime history of opioid dependence, 213 (94.6%) also had a history of OMT. Thus, we cannot distinguish between the suppressive effect of opioid use disorder itself and the specific and distinct effects of different OMT.

The suppressive/protective effect in our sample of a lifetime history of rapid route of administration for cocaine use against the acquisition of significant BD would seem counter-intuitive. However, in this clinical sample, the use of intravenous or smoked *versus* snorted cocaine was also associated with the use of intravenous opioids and the number of opioid dependence criteria. A logistic regression identified 89% of cocaine injectors in our sample with those two variables alone (OR = 2.5, $p = 0.005$, and OR = 1.4, $p < 0.001$). This could suggest a suppressive/protective effect of opioid use and/or treatment on the consequences of rapid effect cocaine administration and requires further investigation in future studies.

The cross-sectional design is the most important limitation of the current study. Consequently, no causal relationship can be ascertained. Our interpretation is the proposed “toxic hypothesis,” whereby greater cocaine use leads to the acquisition of more behavioral disturbances. However, this could also be seen as indicative of more inattentive/behavioral symptoms, leading to more cocaine use, perhaps as a form of self-medication (Mariani et al. 2014). Delineating the relative relevance of these different causal models will be an important goal for future research.

A second limitation arises from those failing to complete the questionnaires that may have differed from those who did complete the questionnaires, including in regard to CD and OMT. Consequently, the study sample may not be representative of patients from an outpatient addiction facility, thereby limiting the generalization of the results.

A third limitation may be seen to arise from the lack of an ADHD diagnosis derived from a structured diagnostic interview. However, as it was not the intention to use an ADHD diagnosis, but rather to use a dimensional tool of similar behavioral measures, the lack of a formal ADHD diagnosis is not a limitation of this study. Clearly, some patients in the sample, perhaps especially WURS+ASRS+ patients, would have met the ADHD criteria. However, this would be unlikely to be the case for all WURS+ASRS+ patients and would not seem to apply to many, if any, of the 74 WURS-ASRS+ patients, who reported emerging “*de novo*” significant behavioral disturbances (WURS-ASRS+). Again, the use of these questionnaires as dimensional tools negates any limitation that could be seen to arise from a lack of ADHD formal diagnosis.

The use of the WURS-25 items and the ASRS-6 items as dimensional scales may be seen as another limitation, as these questionnaires were developed to generate categories via a threshold score for ADHD. Nor were these scales developed to measure behavioral disturbances arising from SUD. However, administering these two scales provides the only

available impulsivity-like scales to give indicants of changes from childhood to adulthood.

Clearly, the measures used do not define childhood or adult ADHD as a DSM diagnosis. However, they do capture an impulsive-inattentive syndrome that may be mixed with conduct or personality disorder features. Indeed, this may be a strength of the study, as the self-report questionnaires assess persistent motor impulsivity, work planning, and attention difficulties, which are BD that are far more frequent than ADHD disorder itself (Dakwar et al. 2012) and may therefore reflect wider everyday difficulties, including in everyday clinical management, including treatment adherence (Pérez de Los Cobos et al. 2011; Delavenne et al. 2011; Kaye et al. 2014). Even if the number of patients concerned by this acquired syndrome is limited, our study may provide new avenues for clinically relevant research.

Ideally, future studies should include a prospective design that would better satisfy the Bradford Hill criteria for causality vs a cross-sectional study (Hill 1965). Clinicians should consider a prospective design to assess the occurrence and persistence of BD over the months and years from the onset of cocaine use, including from the onset of cocaine use disorder. Furthermore, and perhaps more feasibly, clinicians in everyday practice settings could design prospective studies attempting to observe a reduction of those symptoms when patients decrease the amount of their cocaine or stimulant use, as suggested in a recent medication trial (Levin et al. 2018). Such clinical studies would provide further evidence of the temporal relationship between stimulant exposure and the emergence of significant BD. Similarly, the relevance of such emergent behavioral changes arising from the use of other stimulants should be investigated, including amphetamines, methamphetamine, or cathinones. Moreover, specifically designed preclinical behavioral sensitization experiments performing a direct comparison of stimulants and opioids in the same animal model would help to clarify the interactions of stimulant use with opioid use/treatment in the development of emergent behavioral disturbances. Once that the previous studies have established that the chronic exposure to cocaine induces behavioral disturbances in Humans, proof-of-concept studies assessing the efficacy of different pharmacological strategies, including OMT, on the specific dimensions of cocaine-associated BD will be important to determine. Such studies should also be used to test the validity and utility of ADHD scales scores, such as the WURS or the ASRS, as “state” time-sensitive measures, including in association with objective behavioral measures such as actimetry.

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Compliance with ethical standards

Both studies were conducted according to French laws on bioethics. Patients were required to be free of unstable psychiatric conditions and to give free and informed written consent. Both studies were approved by local ethics committees (CPP IDF VI and CPP IDF IV respectively).

Conflict of interest In the last 3 years, outside of the submitted work, FV has received research grants from the Programme Hospitalier de Recherche Clinique from the French Ministry of Health (PHRC National PHRC-N-18-07777), the Fondation pour la Recherche en Alcoologie (Fondation de France), and congress fees from Camurus AB. RI has received honorarium by Pierre Fabre, which was given in full to a non-lucrative association, and honoraria from Lundbeck for giving talks. FB has received honoraria or research or educational conference grants from Bristol-Myers Squibb, Otsuka, Eli Lilly & Co., Servier, Takeda, Sanofi Aventis, Lundbeck, AstraZeneca, and the European Space Agency and has received peer review research funding from the Ministry of Research, Assistance Publique-Hôpitaux de Paris, the National Institute for Research (INSERM), and the NARSAD, outside the submitted work. GB has received research grants from Agence Nationale de sécurité du médicament et des produits de Santé (ANSM) and Institut de Recherche en Santé Publique (IRESP) and congress fees from Camurus, Indivior, and Bouchara. Other authors have nothing to disclose.

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