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Stabilité psychométrique des critères diagnostiques du DSM-5 pour les troubles de l'usage de substances et valeur prédictive du craving sur l'usage de substance selon le contexte de soin. Dans quelle mesure le craving diffère-t-il des autres critères diagnostiques ?

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THÈSE PRÉSENTÉE
POUR OBTENIR LE GRADE DE
DOCTEUR DE
L'UNIVERSITÉ DE BORDEAUX

ÉCOLE DOCTORALE SCIENCE DE LA VIE ET DE LA SANTÉ
SPÉCIALITÉ NEUROSCIENCES

Par Charlotte KERVRAN

Stabilité psychométrique des critères diagnostiques du DSM-5 pour les troubles de l'usage de substances et valeur prédictive du *craving* sur l'usage de substance selon le contexte de soin. Dans quelle mesure le *craving* diffère-t-il des autres critères diagnostiques ?

Sous la direction de : Marc AURIACOMBE

Soutenue le 18 décembre 2019

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TITRE : Stabilité psychométrique des critères diagnostiques du DSM-5 pour les troubles de l'usage de substances et valeur prédictive du *craving* sur l'usage de substance selon le contexte de soin. Dans quelle mesure le *craving* diffère-t-il des autres critères diagnostiques ?

RESUME

Introduction

La perte de contrôle de l'usage d'un objet source de gratification est au centre de la définition de l'addiction ou trouble de l'usage. La validité psychométrique des critères diagnostiques du trouble de l'usage de substances du DSM-5 a pu être testée pour plusieurs substances, mais l'ajout du *craving* et sa place comme critère diagnostique fait encore débat. Par ailleurs, un modèle de l'addiction a été proposé dans lequel les variations du *craving* comme phénomène dynamique seraient prédictives de la rechute, appuyant son ajout comme critère diagnostique de la perte de contrôle de l'usage. Cependant les études, à ce jour ont porté uniquement sur des échantillons d'usagers de substances dans une démarche de réduction de l'usage ou d'abstinence.

L'objectif principal de ce projet de thèse est de tester la stabilité psychométrique des critères diagnostiques du trouble de l'usage du DSM-5 selon le contexte de soin, en apportant une attention particulière au rôle du *craving*, d'une part comme critère diagnostique, et d'autre part comme phénomène prédictif de l'usage. Des usagers de substances, recrutés dans des programmes de réduction des risques (HR), un environnement propice à l'usage, ont été comparés à des usagers de substances en demande traitement (TX) de réduction de l'usage ou d'abstinence.

Méthode

La stabilité des 11 critères diagnostiques du trouble de l'usage de l'alcool, de la cocaïne, des opiacés, du cannabis et du tabac a été testée. Des analyses *d'Item Response Theory* (IRT) et le *Differential Item Functioning* (DIF), ont permis d'étudier le comportement des critères diagnostiques entre eux et par rapport au trait latent sous-jacent du trouble de l'usage, et de tester le fonctionnement des critères entre les deux populations. L'applicabilité du modèle de l'addiction a été testée parmi des sujets HR avec la méthode EMA (*Ecological Momentary Assessment*) qui recueille l'intensité du *craving* et l'usage de substance de façon répétée en vie quotidienne. La méthode HLM (*Hierarchical Linear Model*) a été utilisée pour analyser les liens prospectifs.

Résultats

Quels que soient la substance et le contexte de soin, les critères diagnostiques évaluant la perte de contrôle de l'usage, à la différence des critères diagnostiques de conséquences de l'usage, fonctionnent correctement et plus particulièrement le critère "*craving*". Ce nouveau critère apparaît comme le critère le plus sélectif, car il s'ajuste le mieux au modèle à un facteur, il est parmi les plus fréquents, il a un pouvoir discriminant plus marqué que les autres critères et il repère les sujets avec un trouble de l'usage de substance peu sévère. L'EMA met en évidence le rôle prédictif du *craving* sur l'usage, quel que soit le contexte d'usage.

Conclusion

Ce travail remet en question la pertinence des critères de conséquences de l'usage, de par leurs caractéristiques psychométriques moins performantes que les critères de perte de contrôle, et leur faible stabilité inter-échantillon. Ce travail souligne le rôle du *craving* comme moteur de l'usage et appuie son intérêt comme mesure diagnostique et pronostique de la perte de contrôle. Ces résultats pourraient faire de lui un marqueur spécifique et précoce de l'addiction facilement détectable et utilisable en clinique, et justifient qu'il puisse être une cible à privilégier des interventions thérapeutiques.

Mots clés : Addiction, *craving*, neurosciences comportementale, diagnostic, critères diagnostique

TITLE: Stability of the psychometric characteristics of the DSM-5 diagnostic criteria for substance use disorders and the predictive value of craving for substance use according to treatment context. How does craving differ from other diagnostic criteria?

ABSTRACT

Introduction

Loss of control of use of a rewarding substance is the core of substance use disorders. The psychometric validity of the DSM-5 diagnostic criteria for substance use disorders was tested for several substances, but the addition of craving as a diagnostic criterion is still debated. A model of addiction has been proposed in which craving intensity fluctuation over time predicts later use and relapse supporting its addition as a diagnostic criterion of the loss of control dimension. However, these previous studies focused only on samples of substance users attempting to reduce use or abstain.

The main objective of this thesis project is to test the psychometric stability of the diagnostic criteria of the DSM-5 substance use disorders according to treatment context, paying particular attention to the role of craving as a diagnostic criterion and as a dynamic dimension. Substance users recruited in harm reduction programs (HR), a substance-use friendly environment and substance users seeking treatment (TX) to reduce or abstain from use were compared.

Methods

The stability of the 11 diagnostic criteria for alcohol, cocaine, opiates, cannabis and tobacco use disorders was tested. The Item Response Theory (IRT) and Differential Item Functioning (DIF) analyses made it possible to study the behavior of the diagnostic criteria between them and in relation to the underlying latent trait of the use disorder, and to test the functioning of the criteria between the two populations. The applicability of the model of addiction was tested among HR subjects using the EMA (Ecological Momentary Assessment), collecting craving intensity and substance use repeatedly in daily life, to test the prospective link using the HLM (Hierarchical Linear Model) method.

Results

Regardless of substances used and treatment context, the diagnostic criteria assessing loss of control worked correctly and more particularly the craving criterion, which was less the case for the diagnostic criteria related to consequences of use. As a diagnostic criterion, craving seems to be the most selective, because it fits better to the one-factor model, it is among the least difficult to be endorsed (more frequent), is the most discriminant and captures subjects with mild substance use disorders. The EMA study highlights the predictive role of craving on use, regardless of the context of use.

Conclusion

This work questions the relevance of the criteria of consequences of use, because of their psychometric characteristics, which are less effective than the loss of control criteria, and their low inter-sample stability. This work highlights the role of craving as a driving force for use and supports its interest as a diagnostic and prognostic measure of loss of control. These results could make it a specific and early marker of addiction that can be easily detected and used in clinical practice, and justify its being a target for therapeutic interventions.

Keywords: Addiction, craving, behavioral neuroscience, diagnosis, diagnostic criteria

Unités de recherche

Ce travail de thèse a été réalisé dans le laboratoire SANPSY en collaboration avec deux laboratoires américains.

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Un séjour dans l'équipe de recherche du Professeur D. Metzger et du Dr. C. Denis à l'université de Pennsylvanie m'a permis d'acquérir des compétences particulières dans le l'étude et le recrutement de sujets injecteurs en milieux de réduction des risques.

La collaboration avec le laboratoire du Professeur D. Hasin et du Dr. D. Shmulewitz de l'université de Columbia, a permis d'acquérir des connaissances approfondies des analyses IRT et de leur interprétation.

Financement de la thèse

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SYNOPSIS

Introduction

Substance use disorder (SUD) or Addiction is defined as the loss of control of use of a reinforcing substance, that translates into the persistence of use despite the accumulation of negative consequences. The psychometric validity of the current DSM 5 diagnostic criteria was tested using the Item Response Theory (IRT) analyses, in general population and clinical samples, but the addition of craving as a diagnostic criterion is debated. Justifications for adding craving included the view that it is central to SUD and that it can lead to relapse. Using Ecological Momentary Assessment (EMA), a model of addiction was proposed in which cues in daily life produce later craving intensity fluctuations that predict later use and relapse making craving a potential proximal marker of addiction.

However, both Psychometric studies of diagnostic criteria and EMA studies have been done with subjects in treatment attempting to reduce or abstain. This specific care context may have influenced some of the current results. It is important to study how results to date are generalizable to samples of substance users in an environment that does not promote change in use through addiction treatment.

Objective of the thesis

The main objective of this thesis project was to test the psychometric stability of the diagnostic criteria for the DSM-5 substance use disorder and craving's predictive value on substance use, across different care settings : substance users attempting to reduce or abstain from use in treatment setting and substance users not attempting to reduce or abstain from use, outside treatment settings.

To model subjects attempting to reduce or abstain from use in treatment settings (Tx), we chose the subjects of the ADDICTAQUI cohort, a prospective cohort for patients with addiction who are seeking treatment in specialized addiction centers.

To model substance users not attempting to reduce or abstain from use we chose substance users in Harm Reduction (HR) setting that do not promote substance use reduction. Substances user in HR settings seek support for safer use to decrease consequences of substance use in substance-use-friendly environments. We used the COSINUS cohort, a prospective cohort of regular injectors of illegal substances recruited in Harm reduction settings (manuscript 1).

Manuscript 1: Impact of drug consumption rooms on risk practices and access to care in people who inject drugs in France: the COSINUS prospective cohort study protocol.
BMJ Open, 2019.

The specific objectives examined in this thesis were organized into three main parts: a literature review and two experimental parts.

Part I aimed to conduct a systematic literature review to describe the state of current knowledge on the diagnostic characteristics of addiction and craving, among active substance users recruited in Harm Reduction settings (HR) and to examine how these factors related to excessive and problematic use and risk behavior (manuscript 2).

Part II aimed to test the psychometrics stability of the 11 criteria of DSM-5 substances use disorder by care settings. To achieve this part, the dimensionality and psychometric validity of the 11 DSM-5 criteria for alcohol, opiates, cocaine, cannabis and tobacco use disorders, with a focus on craving, were evaluated among Tx current substances users (manuscript 3). Then, a comparison of current HR and Tx users of alcohol, opiates, cocaine, cannabis and tobacco on substance use disorder (SUD) diagnostic characteristics, and craving frequency and intensity in past 30 days was conducted (manuscript 4). Finally, to examine the psychometric stability of

diagnostic criteria for Substance Use Disorders (SUD) by care settings, differential criteria and test functioning were tested between HR and Tx samples (manuscript 5).

Part III aimed to examine the predictive value of craving on substance use among HR substances users. The objectives were to examine the prospective link between cues, craving and substance use among active substances users recruited in HR setting (manuscript 6).

PART I: Systematic literature review: Diagnostic Criteria for Substance Use Disorders Among Substance Users in Risk Reduction Programs

Manuscript 2: Diagnostic characteristics of addiction and craving among active substance users in Needle exchange programs and supervised injection facilities: a review of the literature. (submitted in review)

Aims

To describe the state of current knowledge on the diagnostic characteristics of addiction and craving, among individuals who use substances recruited in Harm Reduction programs (HRP) and to examine how these factors related to excessive and problematic use and risk.

Methods

This review is an examination of the literature. Relevant literature was selected from online PubMed and PsycInfo database up to January 5, 2019. We considered all studies that included individuals who use substances in HRP and assessed information on diagnostic characteristics of addiction, or craving.

Results

Among the 190 articles retrieved, 11 met criteria for inclusion: 3 examined craving and 8 use disorder diagnostics. All individuals met criteria for opiate use disorder, 68% for alcohol and 79% for cocaine use disorders. Among study selected participants, 57.4% rated craving as moderate or severe and 2 studies suggested an association between craving and HIV risk practices. The overall quality of studies was low, due to lack of details on diagnostic criteria and lack of prospective studies to better assess the link between craving and HIV risk practices.

Conclusions

Among individuals who actively use substances recruited in HRP, prevalence of substance use disorders was high and craving could have an impact on some persistent risk behaviors. Prospective studies are needed.

PART II: The DSM-5 SUD diagnostic criteria and the role of craving as a diagnostic criterion

General methods of psychometric analysis used in manuscripts 3 and 5:

Sample

Substance users who sought Tx (n=1359) and Substance users in HR settings (n=130) in Bordeaux, France, were assessed with the Addiction Severity Index, a visual numerical craving scale and DSM-5 SUD criteria. Analyses were conducted separately for current users (used the substance at least 2 times per week for 12 months): 876 alcohol (Tx n= 787, HR n=89), 233 opiate users (Tx n= 131, HR n=102), 223 cocaine users (Tx n= 141, HR n=82), 599 cannabis users (Tx n= 504, HR n=95) and 1142 tobacco users (Tx n= 1014, HR n=128).

Unidimensionality and Item Response Theory (IRT) models

For each substance, a one-factor confirmatory factor analysis (CFA) model of the 11 SUD criteria confirmed unidimensionality when the model showed adequate fit. Latent variable methods such as item response theory (IRT), are the preferred approach for assessing dimensional and structural validity of the diagnostic criteria. IRT analyses allow evaluation of the psychometric properties of criteria to better understand the behavior of criteria between each other, providing information on criterion difficulty to be endorsed (inversely related to frequency), and discrimination (how well the criterion differentiated between respondents with high and low severity of the latent trait). IRT allows to identify the specificity of particular criteria as indicators of the underlying disorder.

Differential Item Functioning (DIF) & Differential Test Functioning (DTF)

To determine if criterion (item) function differed based on key subject characteristics and care settings, multiple indicator multiple cause (MIMIC) structural equation models were used to model each DSM-5 criterion set as a latent variable indicated by the 11 criteria and regressed on the participant characteristics. DIF was indicated when a criterion showed a statistically significant association with a subject characteristic, after accounting for the underlying association with the latent variable.

To test if the whole 11-criteria set functioned differently by participant characteristic, we calculated the average difference in the expected number of criteria for individuals with the same trait severity by participant characteristic subgroups. A difference smaller than 1 indicates no DTF, since that difference would lead to minimal differential SUD diagnosis by subgroup.

Manuscript 3: Item Response Theory analyses of DSM-5 substance use disorder criteria in French outpatient addiction clinic participants. How much is craving special? (Submitted in review)

Aims

To evaluate the dimensionality and psychometric validity of the 11 DSM-5 criteria for alcohol, opiates, cocaine, cannabis and tobacco use disorders, with a focus on craving, and to evaluate these properties by age, gender and psychiatric comorbidities in a French sample of subjects seeking addiction treatment.

Methods

Cross-sectional study, included participants recruited from outpatient clinics with DSM-5 substance use disorder and sought treatment for at least one addiction. Diagnostic criteria were evaluated with the Mini international Neuropsychiatric Interview. In Current regular user, defined as at least two times per week, of alcohol (n= 787), opiates (n= 131), cocaine (n= 141), tobacco (n= 1014) and cannabis (n= 504), factor and 2-parameter IRT analysis was used to investigate the dimensionality and psychometric properties of the 11 DSM-5 SUD criteria. Differential Item and Test functioning (DIF & DTF) analysis were performed across sociodemographic characteristics and psychiatric disorders.

Results

1359 participants were included (68% male; mean age 38.7). Craving criterion had high prevalence (71% to 87%). One-factor dimensionality was confirmed, excepted for tobacco. Craving criterion had the strongest factor loadings, lower difficulty (range, -1.29 to -0.67) and higher discrimination (range, 2.11 to 3.05), and no DIF compared to other criteria. The tobacco criteria set functioned differently by mood and anxiety disorders.

Conclusions

We confirmed the unidimensionality of the 11 SUD DSM-5 criteria and indicate that craving was the most selective criterion because of its psychometric properties and had no DIF compared to other criteria, regardless of the substance in this adult clinical sample.

Aims

The aim of this study was to compare substance users in harm reduction settings (HR) and SU seeking treatment for addiction (Tx) on substance use disorder (SUD) diagnostic characteristics, and craving frequency and intensity in past 30 days for five substances.

Methods

Substances users who sought Tx (n=1,143) and substances users in HR settings (n=130) in Bordeaux, France were assessed with the Addiction Severity Index, a visual numerical craving scale and DSM-5 SUD criteria. Pearson's chi-squared test was performed for categorical variables and student-t test or a Welch test for continuous variables for univariate analysis and logistic and linear regression models were used to adjust diagnostic characteristics, and craving comparison on sociodemographic and other addiction variables. Benjamini-Hochberg procedure was used to control the false discovery rate.

Results

Analyses were conducted separately for current users (used the substance at least 2 times per week for 12 months) of alcohol (Tx n= 787, HR n=89), opiate users (Tx n= 131, HR n=102), cocaine users (Tx n= 141, HR n=82), cannabis users (Tx n= 504, HR n=95) and tobacco users (Tx n= 1014, HR n=128). HR subjects were younger than Tx (test value, $p < .0001$). There was no significant difference in the prevalence of SUD diagnosis, but the prevalence of diagnostic criteria studied individually was slightly different between HR and Tx. Although the craving diagnostic criterion prevalence was similar in both subgroups and for the 5 substances, craving frequency, but not intensity was significantly lower for cannabis, tobacco and opiates in HR subjects.

Conclusion

SU in harm reduction settings have as much SUD diagnosis than substance users seeking addiction treatment, but the criteria distributions were different according to the care settings. Substance users in harm reduction settings seem to have fewer craving episodes but at equal intensity than subjects seeking addiction treatment.

Aims

To examine the psychometric characteristics of diagnostic criteria for Substance Use Disorders (SUD) between substance users in harm reduction settings (HR) and substance users seeking treatment (Tx).

Methods

Differential Item and Test Functioning (DIF & DTF) analysis were performed to examine differences in the difficulty of endorsement of the 11 diagnostic criteria and to test if the criteria set as a whole (the "test") functioned differently by care settings (Tx vs. HR). To test DIF, multiple indicator multiple cause (MIMIC) structural equation models were used.

Results

Regardless of the substance, "craving", "large amount", "time spent", "tolerance" and "activities given up" criteria had similar functioning by care settings. Little evidence for DIF was found for other criteria. The criteria set as a whole did not function differently by care settings for alcohol, cocaine and tobacco. For cannabis, compared to HR, the Tx subgroup had

a greater number of endorsed criteria. For opiates, compared to HR, the Tx subgroup had a smaller number of endorsed criteria with the same trait severity than Tx subgroup.

Conclusion

The unidimensionality of the 11 DSM-5 criteria and applicability of all criteria and diagnosis was confirmed in this large sample of problematic substance users. While the majority of the loss of control criteria functioned well in both care settings, the criteria related to consequences of substance use had several differential functioning.

PART III: Predictive value of craving on substance use

Manuscript 6: How much does craving contribute to use among substance users not attempting to abstain? Preliminary findings from an ongoing Ecological Momentary Assessment Study in substance users in harm reduction programs (preliminary manuscript)

Aims

The main objective of this study was to examine the prospective link between cues, craving and substance use among substance users recruited in harm reduction programs, an environment that is substance-use-friendly.

Methods

Ecological momentary assessment was used during a 2-week period. Setting Data were collected in a French harm reduction setting. Substance users with sedatives or stimulant addiction were included. Using mobile technologies, participants were questioned four times per day relative to craving, substance use and exposure to either substance-specific cues (e.g. seeing a syringe) or personal cues unique to that individual (e.g. seeing the specific person with whom the substance is used). Hierarchical linear and nonlinear modelling was used to test the prospective link between cues, craving and substance use.

Results

Nineteen subjects were included at this stage of the study out of the 40 planned. As the day of the study progressed, no significant change was observed in the intensity of craving ($t=0.360$, $p=0.723$), and the frequency of substance use ($t=-0.313$, $p=0.758$). The number of cues experienced at any given assessment (T0) was not associated with craving intensity at the next assessment. Craving was associated strongly with concurrent substance use ($t=3.993$, $p<0.001$), and remained a significant predictor ($t=2.332$, $p=0.032$) of substance use up to four hours later on average. Substance use was a strong significant predictor of craving intensity at the next assessment ($t=4.386$, $p<0.001$). When the models were adjusted for age and gender, or on status on the dependent variable at T0, only the prospective value of substance use on craving intensity remained significant.

Discussion

The preliminary results show for the first time, in HR setting, that active substance users, increase of craving intensity predicts increase in probability of main problematic substance use. In addition, our results highlight a bidirectional nature of the craving and substance use association, because substance use is a strong predictor of increase of craving intensity. In this way, the findings underscore the extent to which craving contribute to addiction chronicity even in context of active use. The study needs to be continued because some results could be due to a lack of power and are likely to become significant with more inclusions.

Conclusions

We confirmed in a sample of French adults with problematic substance use recruited in two different care settings the dimensional and structural validity of the 11 diagnostic criteria for the DSM-5 use disorder, previously reported in clinical samples. Our results show that the diagnostic criteria related to loss of control are more stable across the different care settings than the criteria related to the consequences of use in excess. In addition, in the debate on the addition of craving as a diagnostic criterion the results highlight that this criterion is the most selective because of its high frequency and psychometric characteristics. These specific characteristics are stable across care settings and for all substances, making it an important criterion of the diagnosis of substance use disorders. Preliminary findings from the ongoing EMA study suggests that craving expresses a drive for loss of controlled use even when not attempting to reduce use.

This work questions the relevance of the criteria related to consequences of use in excess, because of their psychometric characteristics, which are less effective than the loss of control criteria, and due to their low inter-sample stability. This work highlights the role of craving as a driving force for use and supports its interest as a diagnostic and prognostic measure of loss of control that is core to addiction disorders. Further studies should explore whether craving is a specific and early marker of substance use and addiction disorders.

Publications and communications directly related to the thesis project: 1 manuscript was published, two manuscripts were submitted and are in review, two are in progress to be submitted and 6 orals and/or posters communications in international meetings.

Productions scientifiques

Publications et communications directement liées au projet de thèse

Publié

Impact of drug consumption rooms on risk practices and access to care in people who inject drugs in France : the COSINUS prospective cohort study protocol. M. Auriacombe, P. Roux, L. Briand Madrid, S. Kirchherr, C. Kervran, C. Chauvin, M. Gutowski, C. Denis, M. Patrizi Carrieri, L. Lalanne, M. Jauffret-Roustide, and the Cosinus study group. *BMJ Open*, 2019, 9:e023683.

Soumis

Diagnostic characteristics of addiction and craving among active substance users in Harm Reduction Programs : a review of the literature. Charlotte Kervran, Fuschia Serre, Cécile Denis, Sarah Moriceau, Mélina Fatséas, Perrine Roux, Marie Jauffret-Roustide, Laurence Lalanne, Jean-Pierre Daulouède, Marc Auriacombe. *Substance Abuse*

Item Response Theory analyses of DSM-5 substance use disorder criteria in French outpatient addiction clinic participants. How much is craving special? Charlotte Kervran, Dvora Shmulewitz, Fuschia Serre, Malki Stohl, Cécile Denis, Deborah Hasin, Marc Auriacombe. *Drug and Alcohol Dependence*

En préparation pour soumission

Comparison of substance users seeking treatment and substance users in harm reduction settings on DSM-5 Substance Use Disorder diagnosis. C. Kervran, F. Serre, C. Denis, L. Jakubiec, M. Fatséas, M. Jauffret-Roustide, L. Lalanne, P. Roux, M. Auriacombe.

Do DSM-5 substance use disorder criteria differ by user care settings? An Item Response Theory analyses approach. C. Kervran, D. Shmulewitz, F. Serre, C. Denis, P. Roux, M. Jauffret-Roustide, L. Lalanne, D. Hasin, M. Auriacombe.

Communications (oral et poster)

Characteristics of attenders of safer injecting facilities among people who inject drugs in France: Baseline results from the COSINUS cohort study. C. Kervran C, M. Auriacombe, M. Jauffret-Roustide, L. Lalanne, P. Roux, A. Vilotitch, L. Briand-Madrid, P. Carrieri, C. Denis and the Cosinus group. 79th College on Problem of Drug Dependence, Montréal, Canada 2017.

Addiction-related characteristics of substances users in harm reduction settings: a systematic review. C. Kervran, F. Serre, C. Denis, S. Moriceau, M. Fatséas, P. Roux, M. Jauffret-Roustide, L. Lalanne, J.P. Daulouède, M. Auriacombe. 80th College on Problem of Drug Dependence, San Diego, CA, USA 2018 and Colloque International "Addictions Toxicomanies Hépatites SIDA", Biarritz, France 2019.

Item Response Theory analyses of DSM-5 substance criteria: for alcohol, opiates, cocaine, stimulant, cannabis and tobacco use disorder in 1189 French substance abuse patients. C. Kervran, D. Shmulewitz, M. Stohl, F. Serre, C. Denis, M. Fatséas, D. Hasin, M. Auriacombe.

80th College on Problem of Drug Dependence, San Antonio, TX, USA 2019.

Substance Use Disorder diagnosis and craving: comparison of substance users accessing treatment and substance users in harm reduction programs. M. Auriacombe, C. Kervran, F. Serre, C. Denis, P. Roux, M. Jauffret-Roustide, L. Lalanne, JP Daulouède, M. Fatséas. 81th College on Problem of Drug Dependence, San Antonio, TX, USA 2019.

Are DSM-5 substance use disorder criteria influenced by user treatment environment? An Item Response Theory analyses approach. C. Kervran, F. Serre, C. Denis, D. Shmulewitz, D. Hasin, P. Roux, M. Jauffret-Roustide, L. Lalanne, M. Auriacombe. 81th Colloque International "Addictions Toxicomanies Hépatites SIDA", Biarritz, France 2019.

Does craving predict substance use and infection risk practices? An Ecological Momentary Assessment Study among Needle exchange program participants. F. Serre, C. Kervran, O. Hidden, M. Fatséas, M. Auriacombe. Colloque International "Addictions Toxicomanies Hépatites SIDA", Biarritz, France 2019.

Publications et communications non directement liées au projet de thèse mais liées à la recherche sur l'addiction

Publications

Association between morningness/eveningness, addiction severity and psychiatric disorders among individuals with addictions. C. Kervran, M. Fatséas, F. Serre, J. Taillard, V. Beltran, J. Leboucher, R. Debrabant, J-M. Alexandre, J-P. Daulouede, P. Philip, M. Auriacombe. (2015). *Psychiatry Res*, 229, 1024-1030.

Trouble du sommeil et addictions : impact sur la qualité de vie et le risque de rechute. Fatséas, M., C. Kervran, M. Auriacombe (2016). *La presse médicale* 45: 1164-1169.

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Liste des abréviations

ADDICTAQUI: Addiction Aquitaine cohort

APA: *American Psychiatry Association*

ASI: *Addiction Severity Index*

CFA: *Confirmatory Factor Analysis*

CFI: *Ccomparative Fit Index*

CI: *Confidence Interval*

CIM: Classification Internationale des Maladies

COSINUS: COhorte pour l'évaluation des facteurs Structurels et INdividuels de l'USage de drogues.

DIF: *Differential Item Functioning*

DSM: *Diagnostic and Statistical Manual of Mental Disorders*

DTF: *Differential Test Functioning*

EMA: *Ecological Momentary Assessment*

HLM: *Hierarchical Linear Model*

HR: *Harm Reduction*

ICC: *Item Characteristic Curve*

IM: Indice de Modification

IRT: *Item Response Theory*

MI: *Modification Indice*

MIMIC: *Multiple Indicator Multiple Cause*

MINI: *Mini International Neuropsychiatric Interview*

OMS: Organisation Mondiale de la Santé

RdRD: Réduction des Risques et des Dommages

RMSEA: *Root Mean Square Error of Approximation*

SUD: *Substance Use Disorder*

TIA: *Total Information Area*

TIC: *Total Information Curve*

TLI: *Tucker-Lewis Index*

Tx: *Treatment*

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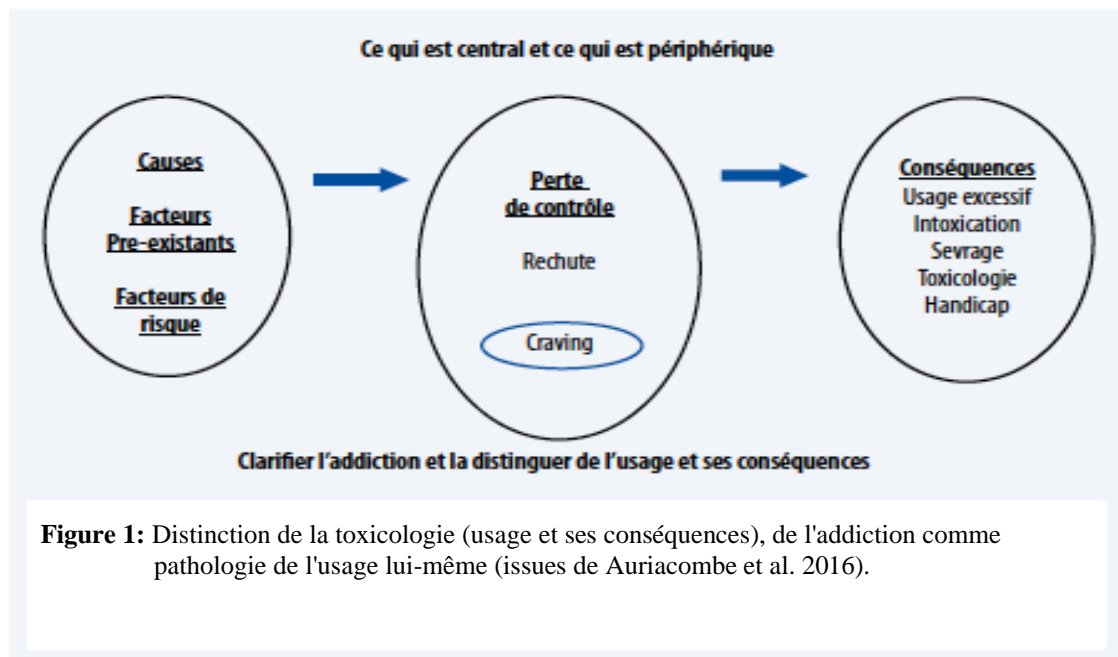
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INTRODUCTION GENERALE

1 Définitions

1.1 L'addiction / trouble de l'usage

Un consensus international se dégage aujourd'hui autour de trois comportements distincts de consommation de substances psychoactives : l'usage simple ou normal, l'usage nocif ou abus, le trouble de l'usage ou addiction (American Psychiatric Association 2000, American Psychiatric Association 2013, The World Health Organization 2018). L'addiction est une modalité d'usage particulière, pathologique. Elle se caractérise par la perte de contrôle de l'usage d'un objet (substance ou comportement) à l'origine source de gratification, et la persistance de cet usage malgré l'accumulation de conséquences négatives qui y sont liées (Auriacombe and Franques 1994, Pickard and Ahmed 2016, Auriacombe, Serre et al. 2018). La définition actuelle de l'addiction se détache des conceptualisations plus anciennes ciblées sur les symptômes induits par la substance (le sevrage et la tolérance) et met en avant l'incapacité de contrôler l'usage, le *craving* (envie irrésistible de faire usage) et la rechute. La rechute se définit comme une reprise non souhaitée d'un usage problématique après une période d'abstinence et est l'expression symptomatique comportementale centrale de l'addiction faisant de lui l'objectif majeur de la prise en charge (Auriacombe, Fatséas et al. 2018). Cette conceptualisation de l'addiction permet de regrouper les addictions liées à l'usage de substances psychoactives légales ou illégales, mais également les addictions sans substances. L'addiction est une condition pathologique stable qui persiste au-delà de l'arrêt, volontaire ou imposé. Cela s'exprime par les rechutes répétées et le *craving*. La perte de contrôle de l'usage est considérée comme le noyau central de l'addiction, qui doit être différencié de la constellation de facteurs de risque et de conséquences préexistants, qu'ils soient toxicologiques, physiques ou environnementaux. Une fois installées, toutes ces caractéristiques coexistent, ce qui rend leur distinction difficile (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018). La distinction de la toxicologie (usage et ses conséquences), de l'addiction comme pathologie de l'usage est un enjeu majeur pour clarifier la cible de l'intervention thérapeutique (Figure 1).



1.2 Le *craving*

Dans l'addiction, le *craving* désigne en français une envie irréprouvable de consommer une substance alors même que l'on ne souhaite pas faire usage de par la conscience des dommages qui y sont liés (Auriacombe, Serre et al. 2016, Sayette 2016). Ainsi, le *craving* tel que nous l'utilisons ici doit être distingué du terme anglais ordinaire qui désigne une envie pas nécessairement pathologique en soi. Dans le cadre de l'addictologie, le *craving* est une envie, un désir, mais anormale. C'est une expérience ego-dystonique qui cause de la détresse et de l'inconfort à ceux qui en font l'expérience. Le *craving* se distingue des phénomènes de sevrage aigus, à la fois par son expression clinique, par les mécanismes physiopathologiques sous-jacents plus directement liés aux systèmes appétitifs motivationnels (Baker, Morse et al. 1986), ainsi que par sa persistance des mois après l'arrêt de l'usage (Mathew, Claghorn et al. 1979, Daughton, Fortmann et al. 1999, Auriacombe, Serre et al. 2016). L'histoire du concept de *craving* est marquée par de nombreux débats, tant sur sa définition, sa mesure, ainsi que sur son implication dans les processus de rechute (Sayette 2016). Il existe également un débat sur le fait que le *craving* requière une reconnaissance consciente du désir de consommer, ou qu'il puisse exister en dehors de la conscience (Sayette, Shiffman et al. 2000, Tiffany and Wray 2012). Néanmoins, même les défenseurs du *craving* reconnaissent l'importance de la nécessité d'améliorer la conceptualisation et l'évaluation de ce phénomène, et de développer une compréhension plus nuancée du lien entre le *craving* et l'usage (Sayette, Shiffman et al. 2000, Tiffany and Wray 2012, Hasin, O'Brien et al. 2013, Sayette 2016).

Le *craving* est un phénomène dynamique dont l'intensité peut varier rapidement au cours d'une même journée, modifiant sa signification et son pouvoir prédictif (Shiffman, Paty et al. 1996, Sayette, Shiffman et al. 2000, Sayette 2016). Des études ont rapporté que les sujets avec une addiction décrivaient souvent des « pics » de *craving* (Drummond, Litten et al. 2000, Tiffany, Warthen et al. 2009). Cela peut être expliqué par le fait que le *craving* est influencé par de nombreux éléments pouvant être des caractéristiques individuelles, des variables liées à la substance et à son usage, et des variables liées à l'environnement (Serre, Fatseas et al. 2015, Serre, Fatseas et al. 2018). De nombreuses études se sont intéressées aux modérateurs du *craving* en vie quotidienne pour voir leur impact direct sur les fluctuations du *craving* au cours du temps (Serre, Fatseas et al. 2015). Le *craving*, bien que considéré comme une caractéristique de l'addiction, et donc par définition observable quel que soit l'objet de l'addiction, pourrait cependant présenter des variations selon le type de substance (Carter and Tiffany 1999), et la sévérité de l'addiction (Shiffman, Hickcox et al. 1997, Shiyko, Burkhalter et al. 2014, Serre, Fatseas et al. 2015). Différents facteurs liés à l'environnement peuvent également influencer le *craving* (Serre, Fatseas et al. 2015), tels que les variables liées à l'interaction avec d'autres individus, comme les conflits, ou la pression sociale (Cho, Ku et al. 2008). Selon le modèle de réactivités aux *cues*, les stimuli associés à l'usage de substance vont devenir, au fil du temps, des indices (*cues*) capables d'induire des réactions conditionnées, dont du *craving*, indépendamment de la présence de la substance (Childress, Hole et al. 1993, Carter and Tiffany 1999, Franques, Auriacombe et al. 1999, Fatseas, Denis et al. 2011, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015). On peut distinguer 2 grands types de *cues*: les *cues* dits « standards » qui vont être les mêmes pour l'ensemble des sujets et sont spécifiques à la nature de l'objet d'usage, comme un briquet, une seringue, une pipe à crack, et les *cues* dits « personnels » qui eux sont propres à chaque individu (être avec Manu, jouer de la guitare, ma boîte en bois) (Conklin 2006, Fatseas, Serre et al. 2015).

L'absence de consensus sur la définition du *craving* a conduit à l'élaboration d'un grand nombre d'outils de mesure très hétérogènes, testés et validés dans des échantillons différents (Rosenberg 2009). La difficulté à définir et à mesurer le *craving* peut en effet s'expliquer par la complexité du phénomène et son aspect multidimensionnel (Shadel et al., 2001). Comme le soulignent des études, en l'absence de mesure universellement acceptée, il convient de choisir l'instrument en fonction de l'objectif de l'étude (Sayette, Shiffman et al. 2000, Sayette 2016). Certains ont critiqué les échelles à un item pour leur manque de sensibilité, cependant il apparaît que les échelles de *craving* à item-unique sont efficaces pour le repérage du *craving* (Tiffany and Wray 2012). Les recherches sur la performance psychométrique des items évaluant le

craving, en particulier lorsque ces items sont utilisés à des fins diagnostiques sont encouragés par plusieurs auteurs (Tiffany and Wray 2012, Hasin, O'Brien et al. 2013, Sayette 2016).

1.3 Le traitement des addictions

Comme pour les autres maladies chroniques, l'objectif de la prise en charge thérapeutique d'une addiction est d'obtenir une rémission la plus stable possible afin que le patient puisse s'adapter à ce nouvel état. Pour cela il existe des moyens thérapeutiques (psychothérapie, pharmacothérapie et éducation thérapeutique) très efficaces, mais qui vont nécessiter une utilisation durable (O'Brien 2008, Fatséas and Auriacombe 2009, Auriacombe, Fatséas et al. 2018). L'objectif propre de la prise en charge d'une addiction est d'agir sur le phénomène de la rechute (Fatséas and Auriacombe 2009, Auriacombe, Serre et al. 2016). En pratique, il s'agit de réduire la fréquence des rechutes et/ou l'intensité de la rechute lorsqu'elle survient. Le cumul des périodes d'abstinence ou de réduction de l'usage permet à long terme de réduire les conséquences négatives de l'usage et donc de gagner en termes de qualité de vie. Le *craving* est une des raisons les plus fréquemment rapportées pour la rechute (Cummings, Jaen et al. 1985, Shiffman, Paty et al. 1996). Dans la mesure où le *craving* est le marqueur pronostic de la rechute, son repérage puis son suivi et son management vont être au cœur de la prise en charge thérapeutique (Auriacombe, Fatséas et al. 2017, Auriacombe, Fatséas et al. 2018).

2 Caractéristiques diagnostiques et modèle de l'addiction

2.1 Le diagnostic du trouble de l'usage selon le DSM

2.1.1 Les grandes classifications et le processus de révision

L'addiction ou le trouble de l'usage est une maladie chronique qui appartient au champ des troubles psychiatriques. Le diagnostic du trouble de l'usage est défini selon une liste de critères, recherchant la présence de symptômes ou manifestations de la maladie, auxquels le patient doit répondre pour être considéré comme ayant le trouble. Pour définir un diagnostic et les critères associés à celui-ci, il existe différentes classifications permettant d'établir un consensus pour tous les professionnels (médical, recherche) du champ des troubles mentaux. Actuellement, il existe deux systèmes de classification prédominants pour les troubles psychiatriques, incluant l'addiction, qui emploient des définitions opérationnelles : le chapitre 6 (Mental, behavioral or neurodevelopmental disorders) de la Classification Internationale des Maladies (CIM) réalisée par l'Organisation Mondiale de la Santé (OMS) et le Manuel diagnostique et statistique des troubles mentaux (DSM) réalisé par l'Association Américaine de Psychiatrie (APA). Ces deux classifications sont souvent comparables, mais pas identiques. La

concordance entre ces deux classifications d'un point de vue psychométrique est très bonne (Bond, Ye et al. 2012). Le système DSM est beaucoup plus largement utilisé dans la recherche et évolue plus rapidement que la CIM (Hyman 2007). Les révisions et changements apportés aux DSM sont basés sur une méthodologie bien précise (Vossart-Guerin 2009, American Psychiatric Association 2013, Gazel, Fatséas et al. 2014). Il faut identifier les problèmes à résoudre. Les solutions proposées doivent être testées pour leur fiabilité et validité comparée à l'ancienne version du diagnostic. Pour être acceptées, des *preuves* doivent être apportées sous forme d'analyses de données. La première édition du DSM a été publiée en 1952 (American Psychiatric Association 1952), et a été suivie de nombreuses révisions prenant en compte régulièrement les avancées de la recherche fondamentale et clinique. Les travaux préliminaires sur le DSM-5 ont commencé à la fin des années 1990 et l'espoir initial était que le DSM-5 ouvrirait la voie à une nosologie fondée sur les neurosciences (Hyman 2007, American Psychiatric Association 2013, Kwako, Momenan et al. 2016, Volkow, Koob et al. 2016). Néanmoins, à l'heure actuelle, l'approche DSM est le système de diagnostic le plus répandu et à la pointe de la connaissance pour les addictions (Auriacombe, Serre et al. 2018). C'est ce manuel qui fixe le cadre des essais cliniques et de beaucoup de protocoles en recherche fondamentale.

2.1.2 *Le trouble de l'usage selon le DSM-5*

Les substances incluses dans les troubles de l'usage du DSM-5 sont : l'alcool, les opiacés, le cannabis, les sédatifs, les stimulants, les hallucinogènes, les inhalants et le tabac (Hasin, O'Brien et al. 2013). Elles ont une importante capacité commune à entraîner un usage excessif générant des conséquences négatives physiques et psychologiques propres à chacune d'entre elles, et à une perte de contrôle. Il est donc important d'avoir un diagnostic valide permettant d'identifier le trouble commun de l'usage de ces substances indépendamment de leurs différences pharmacologiques. Les 11 critères diagnostiques ont été établis pour toutes les addictions aux substances, excepté pour les hallucinogènes et les inhalants qui n'ont pas de symptômes de sevrage (10 critères diagnostiques) (Tableau 1). Pour diagnostiquer un trouble de l'usage, le patient doit présenter un mode d'usage problématique : entraînant une altération du fonctionnement ou une souffrance cliniquement significative, caractérisée par la présence d'au moins deux manifestations (critères), sur une période de 12 mois. Le DSM-5 suggère une classification de ces critères en 4 groupes (Tableau 1) (American Psychiatric Association 2013, Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018). Le premier groupe (perte de contrôle) décrit le noyau de l'addiction, tandis que les trois autres groupes sont considérés

comme périphériques (Tableau 1) (Martin, Langenbucher et al. 2014, Pickard and Ahmed 2016, Auriacombe, Fatséas et al. 2018).

Tableau 1: Critères diagnostiques du trouble de l'usage DSM-5 (American Psychiatric Association 2013, Auriacombe, Serre et al. 2018)

Noyau	La perte de contrôle	(1) Usage de la substance en quantité plus importante ou pendant une période plus prolongée que prévu
		(2) Désir persistant, ou effort infructueux, pour diminuer ou contrôler l'usage
		(3) Beaucoup de temps consacré à des activités nécessaires pour obtenir, faire usage de la substance ou à récupérer de ses effets
		(4) <i>Craving</i> ou envie impérieuse, fort désir ou besoin pressant de faire usage
Périphériques	L'altération du fonctionnement social	(5) Usage répété conduisant à l'incapacité de remplir des obligations majeures au travail, à l'école ou à la maison
		(6) Usage continu malgré des problèmes interpersonnels ou sociaux, persistants ou récurrents, causés ou exacerbés par les effets de la substance
		(7) Des activités sociales, professionnelles ou de loisirs importants sont abandonnées ou réduites à cause de l'usage
	La consommation risquée	(8) Usage répète dans des situations où cela peut être physiquement dangereux
		(9) L'usage est poursuivi bien que la personne sache avoir un problème psychologique ou physique persistant ou récurrent susceptible d'avoir été causé ou exacerbé par la substance
	Les critères d'adaptation pharmacologique*	(10) Tolérance, définie par l'un des symptômes suivants : <ul style="list-style-type: none"> ○ Besoins de quantités notablement plus fortes de substance pour obtenir une intoxication ou l'effet désiré ○ Effet notablement diminué en cas d'usage continu de la même quantité de substances
(11) Symptômes caractérisés par l'une ou l'autre des manifestations suivantes : <ul style="list-style-type: none"> ○ Syndrome de sevrage caractéristique de la substance ○ La substance ou une ayant des effets très proches sont pris pour soulager ou éviter les symptômes de sevrage 		

**Les critères physiologiques/pharmacologiques qui se développent au cours d'un traitement médical approprié ne comptent pas pour un diagnostic de SUD. Ceux-ci peuvent être pris en compte dans le diagnostic de SUD si les substances sont utilisées de façon inappropriée (autre que la façon dont elles sont prescrites).*

2.1.3 Les changements entre le DSM-IV et le DSM-5 et leurs justifications

Des modifications ont été apportées au diagnostic du trouble de l'usage dans le DSM-5, pour régler les problèmes liés au DSM-IV, à savoir la fiabilité et la validité moindres du diagnostic d'abus comparativement au diagnostic de dépendance (Hasin, Schuckit et al. 2003, Saunders 2006), la faible validité du critère des problèmes juridiques et l'absence du critère explorant le *craving*. Ces changements entre la version précédente et le DSM-5 publié en 2013 sont majeurs (American Psychiatric Association 2000, American Psychiatric Association 2013).

Changement du diagnostic : introduction d'une approche dimensionnelle

La classification des critères en 2 diagnostics distincts, la Dépendance et l'Abus du DSM-IV, a été remplacée par un diagnostic unique réunissant l'ensemble des critères : le trouble de l'usage (Tableau 2). La division en deux troubles était guidée par le concept selon lequel le "syndrome de dépendance" constituait une dimension des problèmes liés à l'usage de substance, tandis que les conséquences sociales et interpersonnelles de l'usage excessif en constituaient une autre (l'abus). Le DSM-IV a placé la dépendance au-dessus de l'abus dans la hiérarchie en stipulant que l'abus ne devait pas être diagnostiqué lorsqu'il y avait dépendance (American Psychiatric Association 2000). Les problèmes liés à la hiérarchie de la dépendance à l'égard de l'abus du DSM-IV comprenaient le problème des "orphelins diagnostiques", c'est-à-dire les cas pour lesquels deux critères de dépendance étaient présents en l'absence de critères d'abus, représentant une affection potentiellement plus grave que l'abus, mais non admissible à un des deux diagnostics. La combinaison des deux diagnostics en un seul trouble a réglé ces problèmes (Hasin, O'Brien et al. 2013). De plus, nous sommes passés d'un diagnostic « catégoriel » (absent vs présent) à un diagnostic « dimensionnel » selon un continuum de sévérité. Cela ne remplace pas le diagnostic catégoriel, mais vient le compléter en ajoutant une dimension de sévérité en fonction du nombre de critères rapportés par la personne (Helzer, Bucholz et al. 2007): trouble de l'usage léger (2-3 critères) modéré (4-5 critères) et sévère (6 à 11 critères) (Hasin, O'Brien et al. 2013).

Tableau 2: Comparaison des critères diagnostiques du DSM-IV et du DSM-5 (issue de (Hasin, O'Brien et al. 2013))

	DSM-IV Abuse ^a		DSM-IV Dependence ^b		DSM-5 Substance Use Disorders ^c	
Hazardous use	X	} ≥1 criterion	-	} ≥3 criteria	X	} ≥2 criteria
Social/interpersonal problems related to use	X		-		X	
Neglected major roles to use	X		-		X	
Legal problems	X		-		-	
Withdrawal ^d	-		X		X	
Tolerance	-		X		X	
Used larger amounts/longer	-		X		X	
Repeated attempts to quit/control use	-		X		X	
Much time spent using	-		X		X	
Physical/psychological problems related to use	-		X		X	
Activities given up to use	-		X		X	
Craving	-		-	X		

a Un ou plusieurs critères d'abus au cours d'une période de 12 mois et aucun diagnostic de dépendance ; sauf tabac, pour lequel aucun critère d'abus du DSM-IV n'a été donné.

b Trois critères de dépendance ou plus au cours d'une période de 12 mois.

c Deux critères du trouble de l'usage ou plus au cours d'une période de 12 mois.

d Le sevrage n'est pas inclus pour le cannabis, les inhalants et les hallucinogènes dans le DSM-IV. Ajouté pour le cannabis dans le DSM-5

La première modification dans les critères est l'élimination du critère des problèmes légaux lié à l'usage de substances, au motif qu'une pathologie ne devrait pas être diagnostiquée conformément aux règles et règlements sociaux et sociétaux (Hasin, O'Brien et al. 2013).

Les justifications pour l'ajout du *craving* comme critère diagnostique du trouble de l'usage incluent l'opinion de certains qu'il est au cœur de l'addiction de par son lien avec la rechute, soutenue indirectement par des études comportementales, d'imagerie et des études pharmacologiques et génétiques (Goldstein and Volkow 2002, O'Brien 2005, Fatseas, Denis et al. 2011, Auriacombe, Serre et al. 2016, Auriacombe, Serre et al. 2018). De plus, une raison non empirique d'ajouter le *craving* aux critères du DSM-5 est que les critères de la CIM-10 incluent un critère décrivant le phénomène de *craving*, bien que le mot "*craving*" ne soit pas utilisé en tant que tel, et que son ajout améliorerait la cohérence entre les deux ensembles de critères diagnostiques (The World Health Organization 2018).

2.1.4 L'apport de la psychométrie dans les changements du diagnostic du DSM-5

Les méthodes des variables latentes, comme l'analyse factorielle et la théorie de la réponse aux items (*IRT = Item Response Theory*; (Embretson and Reise 2000)), postulant qu'une construction ou un trait latent, peut être mesuré par un groupe d'items (Embretson and Reise 2000, Langenbucher, Labouvie et al. 2004) (Tableau 3), est l'approche privilégiée pour évaluer la validité dimensionnelle et structurelle des changements apportés aux DSM-5 (Hasin, O'Brien et al. 2013).

L'analyse des traits latents et la théorie des réponses aux items

L'analyse des traits latents permet d'étudier les relations et le fonctionnement d'indicateurs observables (ex : les critères diagnostiques) d'une construction qui ne peut être elle-même observée directement (ex : le trouble de l'usage) (Tableau 3) (Figure 2). L'analyse factorielle est une méthode statistique utilisée pour décrire la corrélation entre des variables observées (critères) et un nombre potentiellement inférieur de variables non observées appelées facteurs (Trait latent/diagnostic). La relation entre les items et le facteur, qui peut s'exprimer par un chiffre variant de -1 à +1 s'appelle la « saturation » (*factor loading*) de l'item sur le facteur. Pour interpréter un facteur, on recherche les items qui ont les coefficients de saturations les plus élevés en valeur absolue (Shmulewitz, Keyes et al. 2011). Pour savoir si tous les items d'une échelle mesurent le même trait latent, il est important qu'ils aient tous des coefficients de

saturation élevés sur ce premier facteur. Pour les ensembles d'items/critères qui forment un trait latent unidimensionnel (un facteur)(Embretson and Reise 2000), les analyses de la théorie de réponse aux items (IRT) fournissent plus d'informations sur la relation entre chaque item et le trait latent par l'intermédiaire de deux paramètres, la difficulté et la discrimination (Tableau 3) (Langenbucher, Labouvie et al. 2004, Shmulewitz, Keyes et al. 2011).

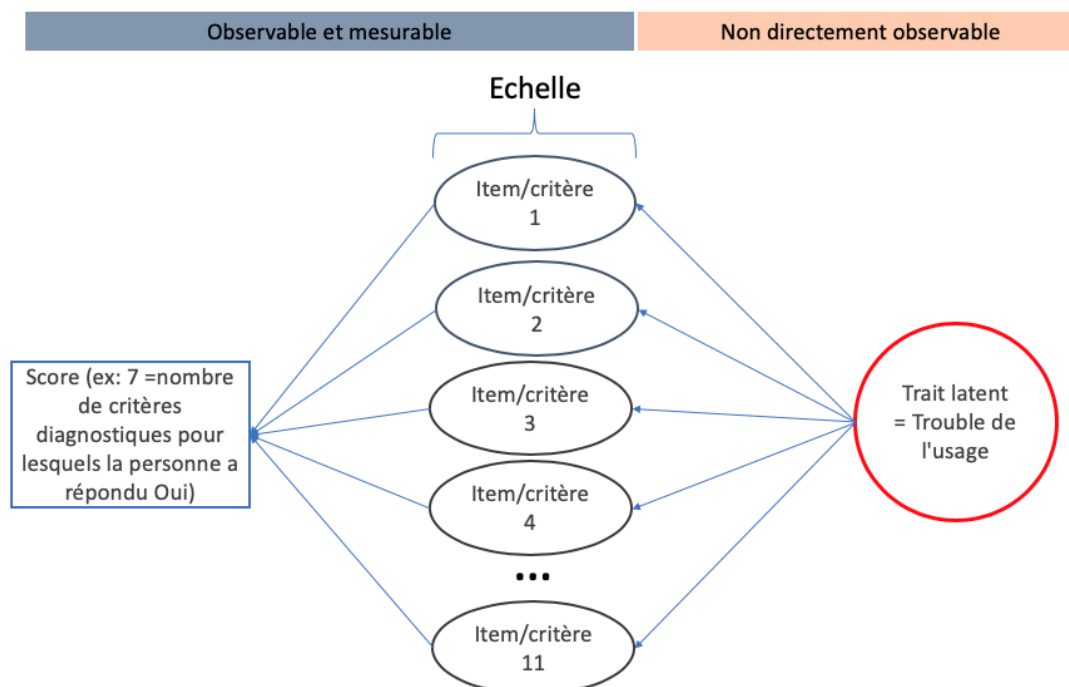


Figure 2: Les 11 critères diagnostiques (symptômes observables) via un score permettent d'évaluer la sévérité du trait latent sous-jacent pour chaque personne (facteur unique).

Parmi les modèles d'IRT, le modèle à 2 paramètres est le plus adapté pour les troubles psychiatriques où les symptômes sont interrogés de manière dichotomique (critère présent, ou absent) par entrevue structurée.

La difficulté d'un item (critère) est inversement corrélée à la prévalence des personnes ayant le critère dans la population étudiée. La difficulté d'un item correspond à la valeur du trait latent sous-jacent auquel 50 % des répondants approuvent l'item (c.-à-d. qu'ils déclarent avoir le critère). La discrimination (ou pouvoir discriminatif) d'un item est un indicateur du degré de précision avec lequel l'item peut distinguer entre les personnes ayant des niveaux de trait latent supérieurs et ceux ayant des niveaux inférieurs au seuil de difficulté de l'item. Une fois la difficulté et la discrimination connues, plusieurs types de graphiques peuvent être générés. La courbe caractéristique de l'item (*item characteristic curve = ICC*) est une fonction logistique en forme de S qui montre la probabilité d'approuver le critère à chaque niveau du trait latent (Figure 3 et 4). Chaque ICC peut être transformée en une courbe d'information d'item (figure 5) en forme de cloche qui indique la quantité d'information psychométrique fournie par un item

à tous les points de la dimension sous-jacente. Les éléments hautement discriminants ont des courbes d'information en pic, fournissant beaucoup d'informations dans une fourchette étroite de sévérité du trait latent autour de leurs seuils de difficulté respectifs. Lorsque les éléments sont calibrés sur un trait sous-jacent commun, leurs courbes d'information d'items sont additives, et le fonctionnement d'un ensemble entier d'items peut être indiqué par sa courbe d'information totale (ou *Total Information Curve = TIC*) (Langenbucher, Labouvie et al. 2004, Shmulewitz, Keyes et al. 2011).

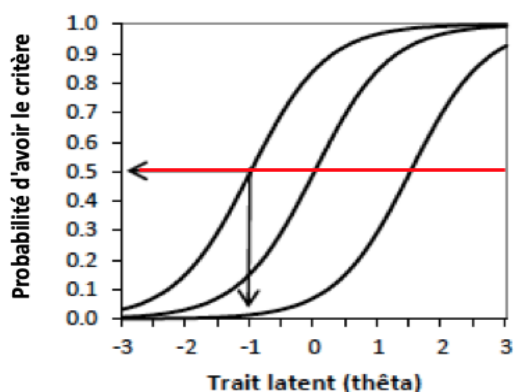


Figure 3: ICC de 3 items ayant une difficulté différente : le critère le plus à gauche est le moins difficile à être approuvé.

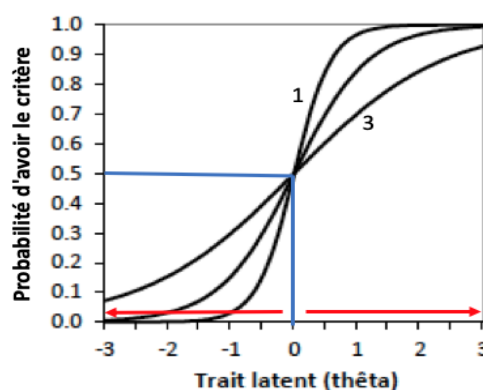


Figure 4: ICCs ayant une discrimination différente : le critère 1 est le plus discriminant (pente la plus raide)

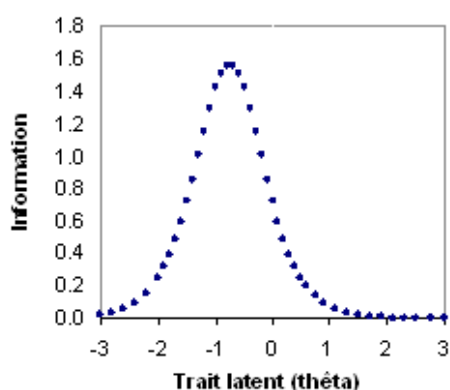


Figure 5: Courbe d'information de l'item ou totale

L'unidimensionnalité du trouble de l'usage

Les analyses factorielles des critères DSM-IV de dépendance et d'abus (sans tenir compte de la hiérarchie du DSM-IV) ont montré que les critères reflétaient un facteur (une construction latente sous-jacente) ou deux facteurs fortement corrélés. Les critères de dépendance et d'abus du DSM-IV étaient répartis sur un continuum de sévérité (trait latent) (Figure 5) (Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015). De plus certaines études utilisant l'IRT ont mis en évidence que certains critères d'abus étaient plus difficiles que certains critères de dépendance (Saha, Chou et al. 2006, Ray, Kahler et al. 2008). Des études explorant les 11 critères du DSM-5, incluant le *craving* et excluant le critère légal, ont confirmé

l'unidimensionnalité du trouble de l'usage, et cela pour de nombreuses substances (Chung, Martin et al. 2012, Hasin, Fenton et al. 2012, Hasin, O'Brien et al. 2013, Preuss, Watzke et al. 2014, Castaldelli-Maia, Wang et al. 2015, Hagman 2017, Marmet, Studer et al. 2019, Serier, Venner et al. 2019).

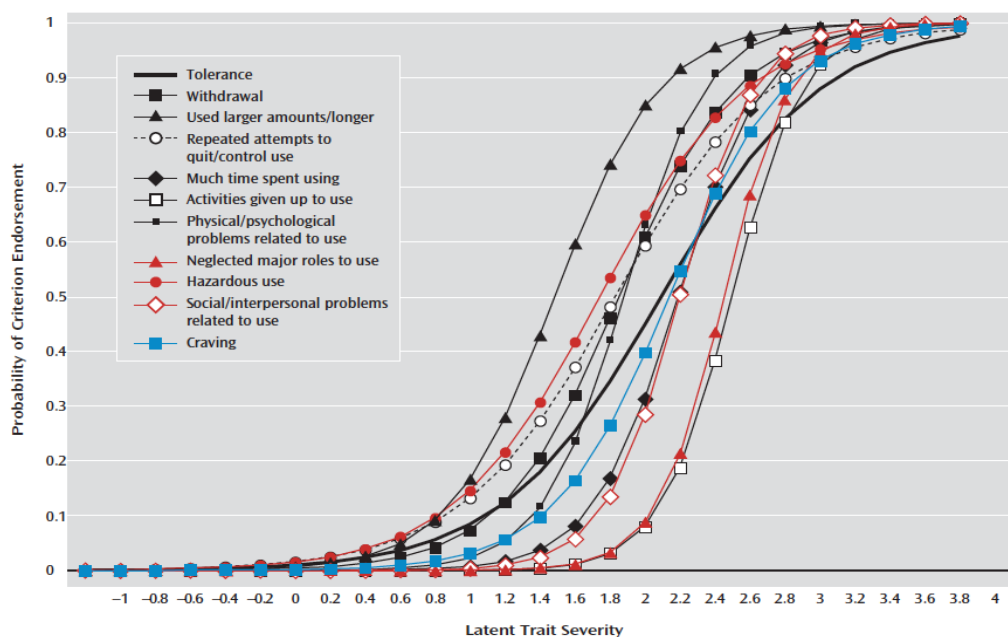


Figure 6: Courbes caractéristiques des 11 critères diagnostiques DSM-5 réparties le long du continuum de sévérité du trait latent (issue de Hasin et al. 2013).

Le retrait du critère « problèmes légaux »

Le critère relatif aux « problèmes légaux » est peu prévalent, très difficile, peu discriminant, s'ajuste peu aux autres critères du trouble de l'usage dans les analyses de facteurs et ajoute peu d'informations au trait latent, justifiant son retrait (Hasin, O'Brien et al. 2013).

L'ajout du critère « craving »

Les résultats des analyses de facteurs et d'IRT ont montré que le critère "craving" s'ajustait bien aux autres critères de la variable latente unidimensionnelle sous-jacente (troubles de l'usage de substance) et que son ajout ne modifiait pas les coefficients de saturation, la difficulté ou la discrimination des autres critères ou du modèle global (Hasin, O'Brien et al. 2013). Cependant, il y a des différences dans le niveau de difficulté dans les analyses IRT entre les études. Dans les études portant sur des populations générales (sujets avec et sans trouble de l'usage), le *craving* avait une difficulté moyenne à élevée (rare) (Cherpitel, Borges et al. 2010, Keyes, Krueger et al. 2011, Gilder, Gizer et al. 2014), et dans d'autres études portant sur des patients avec une addiction aux substances, le *craving* était un critère de difficulté légère (fréquent) comparativement aux autres critères (Hasin, Fenton et al. 2012, Hasin, O'Brien et al.

2013). Ces résultats pourraient s'expliquer par la forte prévalence du *craving* chez les sujets avec addiction comparativement à la population générale (Hasin, O'Brien et al. 2013). Parmi un échantillon de population générale, le *craving* pour les stimulants présentait le coefficient de saturation le plus marqué et était le critère le plus discriminant de tous les autres critères diagnostiques du trouble de l'usage (Gilder, Gizer et al. 2014). Le débat sur son ajout est également lié au fait qu'aucune augmentation significative de l'information totale n'a été observée pour les des substances étudiées (alcool, cocaïne, opiacés et cannabis) une fois ajoutées aux critères de dépendance du DSM-IV. Cela suggère qu'il est largement redondant avec les autres critères (Hasin, O'Brien et al. 2013). Selon les recommandations de la Task Force (groupe de travail) responsable de l'élaboration des critères DSM-5, le *craving* a été intégré, mais une demande de nouvelles études a été formulée afin d'éclaircir le rôle du *craving* d'une part dans le diagnostic et d'autre part dans le comportement addictif (Tiffany and Wray 2012, Hasin, O'Brien et al. 2013, Sayette 2016).

2.2 Rôle du *craving* dans les mécanismes de l'addiction

2.2.1 Intérêt clinique de l'étude du craving

L'étude du *craving* présente un intérêt clinique à différents niveaux. Malgré le débat sur son introduction dans le DSM-5, le *craving* semble avoir sa place dans le diagnostic de par son rôle central dans la perte de contrôle (Hasin, Fenton et al. 2012, Hasin, O'Brien et al. 2013, Auriacombe, Fatséas et al. 2018). Dans les études utilisant le DSM-5, le *craving* a une forte prévalence parmi les personnes ayant une addiction aux substances (Chung, Martin et al. 2012, Hasin, Fenton et al. 2012, Serier, Venner et al. 2019). D'un point de vue thérapeutique, le *craving* est souvent évoqué comme intrinsèquement lié à la rechute et représente donc une cible privilégiée de la prise en charge de l'addiction (Cummings, Jaen et al. 1985, Shiffman, Paty et al. 1996, Cedarbaum and Banta-Green 2016, Auriacombe, Serre et al. 2018). En effet, plusieurs études ont rapporté que le *craving* aurait un rôle précipitant dans de la rechute (Bottlender and Soyka 2004, al'Absi, Hatsukami et al. 2005, Sinha, Garcia et al. 2006). Ainsi, plusieurs médicaments ayant pour but de diminuer le *craving* ont été développés au cours des 30 dernières années, et d'autres traitements initialement substitutifs ou de sevrage ont montré leur efficacité comme médicaments anti-*craving* (Auriacombe, Fatséas et al. 2003, O'Brien 2005, Fareed, Vayalapalli et al. 2010, Reed, Day et al. 2015). Toujours d'un point de vue thérapeutique, le *craving* peut être utile comme indicateur de l'efficacité des traitements, et offrir aux cliniciens une mesure de l'impact de leur prise en charge même quand l'abstinence complète n'est pas atteinte (Tiffany, Friedman et al. 2012, Auriacombe, Serre et al. 2016). Enfin, d'un point de

vue pronostique, le *craving* représenterait un candidat idéal comme marqueur prédictif de la rechute (Ciraulo, Piechniczek-Buczek et al. 2003). D'autres études suggèrent une implication du *craving* dans les comportements de partage de matériel d'injection (Perngmark, Vanichseni et al. 2008).

Bien qu'il soit généralement accepté que le *craving* est un phénomène associé à l'addiction, il existe cependant encore une controverse concernant son rôle dans la prise de substances et dans la rechute. Néanmoins, de nombreux modèles théoriques de l'addiction intègrent le *craving* et proposent une explication de son rôle dans l'usage de substances (pour revue, voir (Skinner and Aubin 2010)). Certains présentent le *craving* comme le substrat motivationnel majeur de la prise de substances et de la rechute lors des tentatives d'abstinence (Marlatt and Gordon 1980, Baker, Morse et al. 1986, Drummond, Litten et al. 2000).

2.2.2 *L'apport de la méthode d'évaluation en vie quotidienne dans les modèles de l'addiction impliquant le craving*

L'étude du craving comme phénomène dynamique

Le *craving* est un phénomène dynamique qui peut présenter des variations rapides au cours d'une même journée et l'intervalle de temps entre le *craving* et l'usage peut-être très court (Serre, Fatseas et al. 2015). L'évaluation répétée peut être utile pour comprendre non seulement l'intensité, mais aussi la durée et les pics de *craving* (Sayette, Martin et al. 2005). De par l'influence de l'environnement et du contexte sur le *craving*, il apparaît nécessaire d'étudier ce phénomène dynamique dans des contextes plus proches des conditions de vie réelle grâce à des méthodes d'évaluation en vie quotidienne.

Définition et principes de la méthode EMA

La méthode EMA (Ecological Momentary Assessment) utilise des appareils de mesure portatifs (smartphones, tablettes) pour mesurer en temps réel des états transitoires d'un sujet évalué dans son environnement naturel, par des mesures répétées dans le temps (Stone and Shiffman 1994). Les mesures proches du temps réel permettent d'éviter les biais de mémoire lors de l'auto-évaluation de phénomènes subjectifs (*craving*) ou objectifs (usage de substances). Les personnes sont capables de se rappeler avec plus d'exactitude des expériences qui viennent de se produire « ici et maintenant » (Ross 1989), alors que l'auto-évaluation et le rappel d'expériences passées sont moins fiables (Bradburn, Rips et al. 1987). Ainsi, la méthode EMA permet de mesurer l'intensité du *craving* en minimisant les biais de mémoire et en examinant l'influence des variations intra-individuelles (Drummond, Litten et al. 2000, Sayette, Shiffman et al. 2000). Les mesures dans l'environnement naturel apportent une bonne validité écologique,

car elle permet d'observer des situations « authentiques » de la vie de tous les jours, c'est-à-dire dans le contexte dans lequel l'expérience se produit naturellement (Brewer 2000). Pour l'étude du *craving*, la méthode EMA permet d'évaluer conjointement un ensemble de variables environnementales susceptibles de modérer l'intensité du *craving* et d'étudier son lien avec l'usage de substances (Drummond, Litten et al. 2000, Sayette, Shiffman et al. 2000, Serre, Fatseas et al. 2015). En répétant les évaluations au cours d'une même journée, la méthode EMA permet d'augmenter la chance d'observer des phénomènes rapides comme les variations de *craving* (Sayette, Martin et al. 2005), tout en mettant en évidence les liens prospectifs entre plusieurs variables qui peuvent se produire sur des temps très courts (Serre, Fatseas et al. 2015).

Le modèle «Cues-Craving-Use»

De nombreuses études ont examiné le caractère prédictif du *craving* sur la rechute grâce à la méthode en vie quotidienne (Serre, Fatseas et al. 2015). L'équipe phénoménologie et déterminant des comportements appétitifs du laboratoire SANPSY a proposé un modèle de l'addiction en se basant sur les résultats obtenus en appliquant la méthode EMA à des personnes ayant une addiction en traitement dans la cohorte ADDICTAQUI (Serre, Fatseas et al. 2012, Fatseas, Serre et al. 2015).

L'intensité du *craving* rapporté en vie quotidienne lors des 2 premières semaines de traitement de l'addiction était prédictive de l'usage de la substance d'addiction, rapporté lors de la même évaluation, et au cours des 3 heures suivantes (Serre, Fatseas et al. 2012, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2018). Ces résultats sont en accord avec de nombreuses études expérimentales (Bottlender and Soyka 2004, al'Absi, Hatsukami et al. 2005, Sinha, Garcia et al. 2006), et observationnelles (Flannery, Poole et al. 2003, Weiss, Griffin et al. 2003, Heinz, Epstein et al. 2006, Allen, Bade et al. 2008, Paliwal, Hyman et al. 2008) et en vie quotidienne (Serre, Fatseas et al. 2015). Les analyses réalisées dans cette étude montraient la nature unidirectionnelle de cette association (le *craving* prédit l'usage lors de l'évaluation suivante, mais pas l'inverse) et soulignaient l'intérêt de disposer de traitements ciblant le *craving* dans le but de maintenir l'abstinence ou une réduction significative de l'usage (Serre, Fatseas et al. 2012, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2018).

Cette étude mettait également en évidence que le nombre de *cues* rencontrés en vie quotidienne était prédictif de l'intensité du *craving* lors du même entretien, et prédictif de l'intensité du *craving* rapporté lors de l'évaluation suivante (Serre, Fatseas et al. 2012, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2018). Ces résultats ont permis de confirmer, en vie quotidienne, les résultats de nombreuses études en laboratoire réalisées chez l'homme et rapportant un lien entre stimuli conditionnés et *craving* pour différentes substances (Childress,

Ehrman et al. 1992, Childress, Hole et al. 1993, Carter and Tiffany 1999, Fatseas, Denis et al. 2011) et sont en accord avec d'autres études en vie quotidienne (Serre, Fatseas et al. 2015).

La méthode EMA a pu mettre en évidence, chez les personnes en traitement pour une addiction, que le *craving* était prédictif de l'usage, en réponse à une exposition à des *cues* associés à l'usage (Figure 7).



Figure 7: Un modèle universel simplifié de l'addiction «*Cues-Craving-Use*». Extrait du chapitre 10 : *Diagnosis of Addiction* du *Routledge Handbook* (Auriacombe, Serre et al. 2018).

3 Les limites de la validité des critères diagnostiques de l'addiction et de la valeur prédictive du *craving* sur l'usage

Il existe encore des débats sur les critères permettant de diagnostiquer l'addiction. Certains auteurs suggèrent que l'addiction devrait être diagnostiquée grâce aux critères centraux évaluant la perte de contrôle plutôt qu'avec des critères plus distaux contingents des conséquences de l'usage en excès (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018). La recherche de biomarqueurs qui caractériseraient spécifiquement le trouble de l'usage de façon unique a donné des résultats, mais finalement aucun n'avait de spécificité suffisante pour une utilisation clinique (Kirmayer and Crafa 2014). Il reste donc important d'avoir des critères diagnostiques permettant d'identifier au plus tôt la maladie avec des marqueurs fiables et les plus proximaux du phénomène étudié. Cela n'étant pas nécessairement des mesures biologiques.

Dans cette perspective la validité psychométrique des 11 critères diagnostiques du trouble de l'usage de substance du DSM-5 a pu être testée de nombreuses fois, dans des échantillons de population générale et en service d'urgence (Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015, Hagman 2017, Marmet, Studer et al. 2019). Dans ces études l'unidimensionnalité des critères est démontrée et l'ajout du critère "*craving*" ne semble pas impacter la construction sous-jacente du trouble de l'usage et les autres critères diagnostiques d'un point de vue psychométrique (Hasin, O'Brien et al. 2013). Bien que la recherche fondée sur des analyses dans la population générale soit importante, cela n'est pas suffisant (Cherpitel, Borges et al. 2010). Ces résultats doivent être reproduits à l'aide de différents ensembles de données, en particulier dans des populations cliniques incluant des personnes avec un usage problématique à une ou plusieurs substances, qui ont tendance à présenter plus de symptômes et des symptômes plus graves que les échantillons de la population générale (Cherpitel, Borges et al. 2010).

Quelques études ont testé la validité psychométrique des critères chez des personnes avec un usage problématique (Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015). Elles ont confirmé les résultats obtenus en population générale, mais peu d'entre elles ont porté un intérêt particulier au nouveau critère "*craving*" (Hasin, Fenton et al. 2012, Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015). L'ajout du *craving* comme critère diagnostique fait encore débat, de par son intérêt dans le diagnostic et ses caractéristiques psychométriques (Tiffany and Wray 2012, Hasin, O'Brien et al. 2013, Sayette 2016). Cependant, certaines études ont montré l'intérêt de l'ajout du critère "*craving*", suggérant l'utilité potentielle de ce critère

comme indicateur précoce du trouble de l'usage (Chung, Martin et al. 2012). Mais de nouvelles études sont nécessaires afin d'éclaircir le rôle du critère "*craving*" pour le diagnostic, mais également le rôle du phénomène *craving* dans le comportement addictif (Tiffany and Wray 2012, Hasin, O'Brien et al. 2013, Sayette 2016). Le modèle « *cues-craving-use* » met en avant le rôle central du *craving* dans l'addiction, car il est associé à son pronostic, appuyant ainsi l'ajout de la recherche de ce phénomène dans les critères diagnostiques. Il a pu être validé pour les addictions aux substances chez des patients en traitement en utilisant la méthode EMA (Serre 2012, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2018). Cependant, les résultats restent très variables d'une étude à l'autre.

Pour valider et généraliser les critères diagnostiques à toutes les situations et populations, il faut savoir si les critères ou les ensembles de critères fonctionnent différemment d'un sous-groupe de population à l'autre. Il y a un fonctionnement différentiel d'un item (*DIF*= *Differential item functioning*) lorsque l'item n'a pas la même relation avec le trait latent sous-jacent dans tous les sous-groupes d'un échantillon (Tableau 3) (Embretson and Reise 2000, Woods, Oltmanns et al. 2009). Cela suggère que des sous-groupes particuliers pourraient être plus susceptibles d'avoir certains critères (Derringer, Krueger et al. 2013, Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015). Les *DIF* peuvent indiquer un mauvais fonctionnement des critères et permettent d'identifier les critères nécessitant un ajustement (Shmulewitz, Greene et al. 2015). Si un nombre suffisant de critères dans un ensemble fonctionnent différemment, cela peut indiquer un fonctionnement différentiel de l'ensemble, c'est-à-dire que des sous-groupes spécifiques de la population seraient plus susceptibles d'obtenir un diagnostic parce qu'ils sont plus susceptibles d'avoir ces critères (Shmulewitz, Greene et al. 2015).

Des différences sur les paramètres des critères entre les études cliniques (Chung, Martin et al. 2012, Hasin, Fenton et al. 2012, Serier, Venner et al. 2019), pourraient être attribuables à des caractéristiques des contextes de soins des personnes, suggérant que les critères diagnostiques pourraient fonctionner différemment selon les contextes de soins.

La plupart des études ont porté sur des échantillons d'usagers qui étaient dans un contexte de traitement orientés vers la réduction de l'usage ou l'abstinence, ou en demande d'un tel traitement, c'est-à-dire dans une démarche de modification de l'usage (Hasin, Fenton et al. 2012, Fatseas, Serre et al. 2015, Serier, Venner et al. 2019). On peut se demander si certains critères diagnostiques ne sont pas spécifiques aux usagers de ces contextes de traitement (Kessler, Molnar et al. 2001), comme le désir répéter de réduire l'usage (Serier, Venner et al. 2019), ou le *craving* souvent décrit comme particulièrement prévalent chez les personnes en

tentative d'arrêt, ou abstinents (Cummings, Jaen et al. 1985, Shiffman, Shumaker et al. 1986). Les conséquences négatives de l'usage, et par conséquent les critères diagnostiques qui y sont associés, sont décrites comme très dépendantes de spécificités individuelles, contextuelles et pharmacologiques (Martin, Langenbucher et al. 2014, Pickard and Ahmed 2016). Cela remet en question leur fonctionnement selon le contexte de soin de la population étudiée. Il se pourrait que les troubles de l'usage de substances soient diagnostiqués selon des critères très différents en fonction du contexte de soins des échantillons cliniques étudiés. Ainsi, il est nécessaire d'explorer les caractéristiques des critères dans des populations de divers contextes de soins (Cherpitel, Borges et al. 2010), pour déterminer s'ils sont influencés par le contexte de soin.

Les études dans des échantillons cliniques ont trouvé des différences de fonctionnement des critères diagnostiques et des tests selon des caractéristiques sociodémographiques et des comorbidités psychiatriques pour les critères du trouble de l'usage DSM-5, y compris le *craving* (Chung, Martin et al. 2012, Hasin, Fenton et al. 2012), mais aucune étude n'a examiné les différences de fonctionnement des critères entre différents contextes de soins.

Les résultats montrant la valeur prédictive du *craving* sur l'usage (Fatseas, Serre et al. 2015), ont été obtenues chez des usagers tentant de réduire leur usage ou de devenir abstinents dans un contexte de traitement. Les résultats concernant le lien entre le *craving* et l'usage de substances (Fatseas, Serre et al. 2015), doivent tenir compte des conditions expérimentales et de la population étudiée (Tiffany and Wray 2012). Qu'en est-il du lien entre le *craving* et l'usage chez des usagers hors du contexte de traitement, orienté vers la réduction de l'usage ou d'abstinence ?

HYPOTHESE ET OBJECTIF

1 Question de recherche

En quoi le fonctionnement psychométrique des critères diagnostiques des troubles de l'usage de substances du DSM-5, et la valeur prédictive du *craving* sur l'usage sont valides et indépendants du contexte de soin ?

2 Objectif scientifique

L'objectif principal de ce projet de thèse est de tester l'influence du contexte de soin sur l'expression de l'addiction en testant la stabilité des caractéristiques psychométriques des critères diagnostiques du trouble de l'usage du DSM-5, et la valeur prédictive du *craving* sur l'usage selon le contexte de soin.

3 Opérationnalisation des objectifs

3.1 Population

Afin de répondre à nos hypothèses, nous avons choisi d'étudier un groupe d'usagers problématiques réguliers de substances recrutés dans deux contextes de soins différents. Nous avons comparé des sujets dans un contexte de traitement de l'addiction, orienté vers la réduction de l'usage similaire aux études prétendantes (Hasin, Fenton et al. 2012, Fatseas, Serre et al. 2015) et des sujets ayant un usage problématique, activement engagés dans l'usage, en dehors du contexte de traitement.

3.1.1 Modélisation des sujets en contexte de traitement

Pour modéliser des sujets en contexte de traitement (Tx) de leur addiction dans une structure dont le soin est orienté vers la réduction ou l'arrêt de l'usage, nous avons choisi les sujets inclus dans la cohorte ADDICTAQUI. Cette cohorte menée par l'équipe Phénoménologie et déterminants des comportements appétitifs du laboratoire SANPSY de l'université de Bordeaux est mise en place depuis 1994 pour étudier les trajectoires de personnes présentant une addiction dans un centre spécialisé en addictologie (CSAPA : Centres de Soins, d'Accompagnement et de Prévention en Addictologie) (Auriacombe Accessed september 2019). Le CSAPA du centre hospitalier Charles Perrens à Bordeaux, rattaché au laboratoire SANPSY, est missionné pour faire un repérage diagnostique médical complet, notamment psychiatrique, et assurer la prise en charge thérapeutique de l'ensemble des addictions avec ou sans substances. **L'objectif du traitement dans cette structure est de maintenir l'abstinence ou la réduction de l'usage afin de réduire et à terme éliminer les conséquences de la perte de contrôle de l'usage. La cible privilégiée du traitement est la perte de contrôle en elle-même et plus spécifiquement le *craving* dans l'objectif de prévenir les rechutes (Auriacombe, Fatséas et al. 2018).** Les usagers de substances inclus dans cette cohorte sont

en demande de traitement de l'addiction, et sont inscrits dans une démarche de modification de leur usage.

3.1.2 Modélisation des sujets en dehors du contexte de traitement

Les usagers de programmes de réduction des Risques et des Dommages (Harm reduction = HR)

Pour modéliser des sujets ayant un usage actif et stable avec une probabilité significative d'avoir un trouble lié à l'usage de substances, en dehors du contexte de traitement orienté vers la réduction de l'usage et/ou l'abstinence et accessible à la recherche, nous avons choisi des participants au programme de réduction des risques et des dommages (Rhodes, Watts et al. 2007, Craine, Hickman et al. 2010, Moracchini, Frauger et al. 2012, Potier, Laprevote et al. 2014, Wilson, Brener et al. 2014, Cadet-Taïrou, Lermenier-Jeannet et al. 2018). La philosophie de la HR tient au fait que l'abstinence n'est pas essentielle pour réduire les dommages (Little, Hodari et al. 2008, Hawk, Coulter et al. 2017). Ce sont les dommages sanitaires, sociaux et légaux causés par l'usage de substances sur les individus, leurs familles et leurs communautés, et non pas nécessairement l'usage de substance lui-même, qui font l'objet de l'attention (Des Jarlais 1995, Little, Hodari et al. 2008, Cadet-Taïrou, Lermenier-Jeannet et al. 2018). Il existe des différences dans la conception et la nature des programmes de réduction des risques, tant entre les pays qu'à l'intérieur de ceux-ci, qui reflètent les facteurs logistiques et politiques locaux (Logan and Marlatt 2010). **Cependant le point commun à ces structures est d'accueillir les usagers de substances, sans exigence de modification de l'usage, pour les accompagner à consommer de façon plus sûre. Un usager de substances, en venant dans un programme de HR tel que les CAARUD (Centres d'Accueil et d'Accompagnement à la Réduction des risques pour les Usagers de Drogues) est en demande d'aide pour réduire les conséquences négatives de son usage problématique, sans pour autant réduire l'usage dans un environnement favorable à l'usage.**

La cohorte COSINUS

À l'occasion de la mise en place en France des Salles de Consommation à Moindre Risque (SCMR) pour les usagers de substances par voie intraveineuse, une cohorte a été mise en place (cohorte COSINUS) (Auriacombe, Roux et al. 2019). L'équipe Phénoménologie et déterminants des comportements appétitifs du laboratoire SANPSY de l'université de Bordeaux est l'un des laboratoires investigateurs principaux de cette cohorte. L'objectif est l'évaluation des besoins de la population d'usagers de substances en termes d'accès aux dispositifs de HR. Les sujets ont été recrutés, à Bordeaux, au sein des CAARUD de la CASE et du CEID.

Manuscript 1: Impact of drug consumption rooms on risk practices and access to care in people who inject drugs in France: the COSINUS prospective cohort study protocol

BMJ Open Impact of drug consumption rooms on risk practices and access to care in people who inject drugs in France: the COSINUS prospective cohort study protocol

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ABSTRACT

Introduction The high prevalence of hepatitis C and the persistence of HIV and hepatitis C virus (HCV) risk practices in people who inject drugs (PWID) in France underlines the need for innovative prevention interventions. The main objective of this article is to describe the design of the COSINUS cohort study and outline the issues it will explore to evaluate the impact of drug consumption rooms (DCR) on PWID outcomes. Secondary objectives are to assess how DCR (a) influence other drug-related practices, such as the transition from intravenous to less risky modes of use, (b) reduce drug use frequency/quantity, (c) increase access to treatment for addiction and comorbidities (infectious, psychiatric and other), (d) improve social conditions and (e) reduce levels of violence experienced and drug-related offences. COSINUS will also give us the opportunity to investigate the impact of other harm reduction tools in France and their combined effect with DCR on reducing HIV-HCV risk practices. Furthermore, we will be better able to identify PWID needs.

Methods and analysis Enrollment in this prospective multi-site cohort study started in June 2016. Overall, 680 PWID in four different cities (Bordeaux, Marseilles, Paris and Strasbourg) will be enrolled and followed up for 12 months through face-to-face structured interviews administered by trained staff to all eligible participants at baseline (M0), 3 month (M3), 6 month (M6) and 12 month (M12) follow-up visits. These interviews gather data on socio-demographic characteristics, past and current drug and alcohol consumption, drug-use related practices, access to care and social services, experience of violence (as victims), offences, other psychosocial issues and perception and needs about harm reduction interventions and services. Longitudinal data analysis will use a mixed logistic model to assess the impact of individual and structural factors, including DCR attendance and exposure to other harm reduction services, on the main outcome (HIV-HCV risk practices).

Ethics and dissemination This study was reviewed and approved by the institutional review board of the French Institute of Medical Research and Health (opinion number:

Strengths and limitations of this study

- ▶ This is the first multi-site harm reduction focused cohort of practices in people who inject drugs (PWID) conducted in France.
- ▶ The study's findings will help to assess the impact of drug consumption rooms and other harm reduction services on HIV and hepatitis C virus risk practices in PWID.
- ▶ The findings will also assess the needs of PWID in France by providing a greater understanding of their social conditions, access to prevention and treatment services.
- ▶ Non-French-speaking PWID are excluded from the cohort so their specific needs are not assessed; they may represent up to 20% of people who attend harm reduction facilities in some sites.

14–166). The findings of this cohort study will help to assess the impact of DCR on HIV-HCV risk practices and other psycho-social outcomes and trajectories. Moreover, they will enable health authorities to shape health and harm reduction policies according to PWID needs. Finally, they will also help to improve current harm reduction and therapeutic interventions and to create novel ones.

INTRODUCTION

Rationale

In France, as elsewhere, people who inject drugs (PWID) faced a dramatic HIV epidemic in the 1990s. In response, the French government's harm reduction policy, which first developed programmes for access to sterile injection material in 1987, extended access in 1994 to include syringe vending machines and the sale of ready-to-use injection kits (Steribox) in community pharmacies,¹ as well as new state-funded

needle exchange programmes (NEP).² These public health initiatives were concomitant with opiate maintenance treatment (OMT) programmes with methadone (available since 1994) and buprenorphine (available since 1995)^{3,4} and HAART for HIV-infected individuals.⁵ HIV prevalence in PWID dramatically decreased from 40% to 20% in 14 years from 1988 to 2002,^{2,6} with a prevalence in 2011 of 10%.⁷ An estimated 77% to 85% of opioid-dependent individuals in France are currently treated with OMT.⁷

Despite this progress, and just as in many countries where OMT and NEP are available,⁸ the impact of this harm reduction policy on the hepatitis C virus (HCV) epidemic in France has not been as great as that for HIV.^{9–12} This is because this policy was adopted when HCV prevalence was already too high to be rapidly controlled. In 2011, HCV infection prevalence in the country was 64% among many PWID.⁷ HCV incidence was also very high, between 11% and 22%,¹³ compared with neighbouring countries such as the Netherlands.¹⁴ The delay in implementing an efficient harm reduction policy may explain the persistent high national prevalence of HCV in PWID today.¹⁵ Besides HCV and HIV infections, numerous other physical problems can result from injecting drug use, including soft tissue infections,^{16,17} cardiovascular and pulmonary complications,¹⁸ and bacterial and fungal infections.¹⁹ In addition, research on existing drug consumption rooms (DCR) showed that they improve access to primary healthcare and improve safer injection conditions.²⁰ By attracting the most marginalised PWID,²¹ they also reduce the level of public injection and so the number of used syringes has dropped in public spaces.²² Finally, it has also been shown that DCR are effective in reducing fatal overdoses.²³

Despite the French health authorities' reluctance to open DCR for many years, mostly because of the country's persistent repressive policy towards drug use and general negative public opinion,²⁴ their success in other countries encouraged the French government to reconsider DCR as a possible additional harm reduction (HR) tool. Two DCR, in Paris and Strasbourg, were opened in 2016 as part of a 6-year experiment granted on the condition that the health and social impact of the facilities would be rigorously evaluated. These two DCR accept all PWID 18 years or older and provide the following services: the possibility to administer drugs by injection (or inhalation in some cases, only for PWID), access to social, medical and psychiatric consultations, the provision of sterile equipment, the collection and disposal of used injection equipment, primary care, harm reduction counselling and HCV, hepatitis B virus (HBV) and HIV testing. In this perspective, the COSINUS cohort (COhort to identify Structural and INdividual factors associated with drug Use) was set up in 2016 to prospectively evaluate the impact of DCR on the reduction of risk-taking behaviours in PWID.

The main objective of this article is to describe the design of the COSINUS cohort study and outline which

issues it will explore to evaluate the impact of the DCR on PWID outcomes.

Research objectives and hypothesis

The main objective of COSINUS is to evaluate the impact of regular DCR use on HIV and HCV risk practices. The hypothesis is that PWID with regular access to DCR have fewer practices at risk of HCV and HIV transmission than PWID with no access. It will also investigate the impact of regular DCR use on access to care. Furthermore, data from COSINUS will be used to study the impact of other individual (eg, age, gender, ethnicity, housing) and structural (eg, exposure to social services, harm reduction services including education about safer injection)²⁵ factors on several outcomes (other risk practices, criminality, current drug use, negative life events, etc.). More specifically, it will help provide a greater understanding of the combined effect of different harm reduction services on PWID health and risk practices.

METHODS AND ANALYSIS

Study design

This prospective, multi-center cohort study, which started in June 2016, will enrol a total of 680 PWID by October 2017 in four different French cities with different geographical and health characteristics (Bordeaux, Marseilles, Paris and Strasbourg). The study design and data collection tools were partly inspired by an evaluation of the Vancouver Downtown Eastside DCR (Insite)²⁶ and the Vancouver Injection Drug User Study.²⁷ Individual follow-up will last 12 months. PWID in the DCR in Paris and Strasbourg constitute the 'treatment' group (hereafter 'DCR-exposed'), while PWID already enrolled in harm reduction programmes constitute the 'control' group (hereafter 'DCR-unexposed'). These four cities were chosen because they were all candidates for the opening of DCR when the law permitting experimentation with DCR passed (Public Health Law from January 2016). Data collection consists of face-to-face interviews (each lasting approximately 20–35 min) administered by a trained interviewer at baseline, 3 months, 6 months and 12 months. Data collection is coordinated by the logistics department of methodology and management (CMG) of ORS PACA – INSERM-IRD UMR1252 (SESSTIM) in Marseilles, under the supervision of the cohort's four PIs (Marc Auriacombe for Bordeaux, Perrine Roux for Marseilles, Marie Jauffret-Roustide for Paris and Laurence Lalanne-Tongio for Strasbourg), and is managed by each site investigator. Participants are compensated for their time with €10 worth of service vouchers after each of the four interviews.

Participants

Subjects were eligible if they self-reported injecting illicit drugs except cannabis (heroin, cocaine/crack, amphetamines, ecstasy) and/or prescription drugs (methylphenidate, buprenorphine, benzodiazepines, morphine

sulfate, oxycodone, methadone) at least once during the previous month. Participants must be over 18 years old and French-speaking. There are no specific exclusion criteria, except if the PWID does not fulfil the inclusion criteria, for example non-French-speaking PWID are excluded. Participants must also provide informed consent to participate in the study. They were recruited mainly in the DCR (in the cities where there is one) and in other harm reduction facilities that currently outreach to PWID likely to attend a DCR if available in each city. This mix of recruitment sites was chosen in order to be able to compare PWID between cities. To avoid duplicate enrollment, the month, year and place of birth are recorded for each participant.

Measures

The evaluation of DCR is based on the following main outcome: the proportion of participants reporting at least one injection-related HIV-HCV risk practice (sharing of syringes/needles, sharing of other injecting paraphernalia (filter, swab, water, cup, etc.)) in the previous month.

The other variables that will be collected are: socio-demographic characteristics (gender, age, housing, employment, living in a couple, ethnicity, parenthood, social allowances, country of birth); history of drug use (age at first drug use, first injection and related context); current drug and alcohol use (type, frequency, quantity of drugs used, context of drug use, use disorder diagnostic criteria, craving); overdoses and suicide risk; drug use-related HIV-HCV risk practices (injecting, snorting, smoking, sharing and reusing injecting equipment); addiction treatments; DCR attendance; health conditions and access to care and prevention (type and frequency of care, satisfaction with care, HIV, HCV and HBV screening and self-reported HIV and HCV status, education in injection, other HR services); criminality (illegal activities and experience of prison); negative life events (violence, sexual assault, loss of a relative, etc.); psycho-social assessment (anxiety, ADHD, PTSD, etc.); injection initiation (experience and context); cognitive assessments (GONOGO, mnesic test); sexual health (sexual risk practices, contraception); discrimination and life course (parents, childhood).

This interview questionnaire includes the full version or some items from several already validated questionnaires as follows: (1) the Blood-Borne Virus Transmission Risk Assessment²⁸ to evaluate the risk practice; (2) a section of the Addiction Severity Index, which is a multi-dimensional questionnaire that measures drug use based on participants' self-report^{29,30}; (3) the Alcohol Use Disorders Identification Test (AUDIT-C) questionnaire to measure alcohol consumption³¹; (4) a set of questions from the PRIMER study to examine injection initiation³²; (5) three validated questionnaires to measure psychiatric outcomes: the 25-item Wender Utah Rating Scale for attention-deficit/hyperactivity disorder screening,³³ the Beck Anxiety Inventory to measure anxiety³⁴ and the Post-traumatic stress

event questionnaire^{35,36}; (6) finally, two questionnaires measure participants' cognitive ability: the go-no go task³⁷ and the mnesic test.³⁸

Table 1 displays the schedule for each assessment.

Sample size

The main outcome is the comparison of the percentage of PWID reporting at least one injection-related HIV-HCV risk practice during the previous month between the DCR-exposed and DCR-unexposed groups. The sample size needed was calculated according to this main outcome. Many studies from different countries with DCR have shown that between 30%^{39,40} and 60%⁴¹ of users regularly attend them (at least once a week). In the French context, the proportion of PWID reporting at least one injection-related HIV-HCV risk practice varies according to the context and the characteristics of PWID recruited in different studies, from 25%²⁵ to 50%.⁴² We hypothesise 33% of regular (ie, at least once a week) DCR attending participants will report at least one of these events. Supposing that one-third of participants will regularly attend DCR, with an alpha=5% and a power of 80%, we need a total of 131 participants in each group. Given an expected attrition rate of 40% after 12 months of follow-up,⁴³ the sample size is therefore 680 (Paris=250, Marseilles=200, Bordeaux=150, Strasbourg=80).

Statistical methods

COSINUS was developed to show the impact of DCR on HIV-HCV risk practices. Longitudinal data analysis will use a mixed logistic model to assess the impact of individual factors (socio-demographic, behavioural and cognitive data) and structural factors, including DCR attendance and exposure to other HR services (access to OMT, social services, education to safer injection, etc.), on the main outcome (reporting at least one injection-related HIV-HCV risk practice during the previous month). Data analysis will be carried out with logistic regression models for qualitative data in two ways: multinomial regression for qualitative data of more than two terms or linear regression for continuous data. In addition, to study the impact of the combined effect of different services (DCR, education about safe injection, other HR services) on the main outcome, we will use mixed-model regression analysis by adjusting for these different structural factors and other covariates. A Cox model-based approach (or duration models) will be used to study the impact of DCR attendance (or other HR services) for a certain event at a certain time (transition from injection to another mode of use, access to care). To take into account bias due to missing data and loss to follow-up, we will perform sensitivity analyses using the Heckman model, which adjusts for this potential source of statistical bias.⁴⁴ Analyses will be performed using several statistical software packages (SPSS V.12.0, Intercooled Stata V.10.0 and SAS; statistical V.10.0).



Table 1 Summary of data collection at each follow-up visit

	M0	M3	M6	M12
Socio-demographic characteristics	x	x	x	x
Socio-economic characteristics	x	x	x	x
History of substance use	x			
Current drug use	x	x	x	x
Alcohol and tobacco use	x	x	x	x
Overdoses and suicidal risk	x		x	x
Drug use-related HIV-HCV risk practices	x	x	x	x
Addiction treatment	x	x	x	x
Health conditions and access to care	x		x	x
Screening for HIV and HCV	x		x	x
Criminality	x	x	x	x
Prison experience	x		x	x
Negative life events	x			x
Initiation injection	x		x	x
HR services user satisfaction	x		x	x
Sexual health		x		
Other practices at risk of dermal contamination		x		
DCR attendance and other services	x	x	x	x
Life course		x		
Attention Deficit Hyperactivity Disorder		x		
Anxiety: Beck anxiety inventory			x	
Post-traumatic stress disorder			x	
Discrimination		x		
GONOGO Task		x		x
Mnemonic Test		x		x

DCR, drug consumption rooms; HCV, hepatitis C virus; HR, harm reduction.

Patient and public involvement

Although participants did not directly contribute to the design of the study or to the development of the research questions, their needs and preferences were considered throughout the process. Feedback to the participants regarding scientific results, will be organised on each study site.

DISCUSSION

The COSINUS cohort study is the first in France designed to assess the impact of DCR on HIV-HCV risk practices. It is important to note that DCR in France are seen as an additional tool to existing NEP and OMT programmes, as well as the recently education programme for safer injecting practices.²⁵

To date, most of the data published on the effects of DCR are from the Vancouver INSITE research team,⁴⁵ whose work greatly contributed to the preliminary design of our cohort study. However, the French and Vancouver contexts are very different in terms of substances available on the black market, access to OMT, sharing practices,

sero-prevalence of HIV and HCV, and harm reduction policy. In France, an estimated 180 000 drug users are currently on OMT,⁴⁶ corresponding to an estimated coverage of 80% in urban areas.^{7 25} Two-thirds of individuals receiving OMT are treated with buprenorphine. This figure contrasts with other high-level income countries, where methadone is more accessible.⁴⁷ This high coverage of OMT may have played a role in decreasing long-term HCV prevalence over recent years.^{2 9-11} The decrease in prevalence of HCV has been slower than that seen for HIV. This reflects the situation in other European countries such as the Netherlands and Switzerland.⁴⁸ Overall, despite high coverage of prevention and treatment services, HCV prevalence data suggest that PWID, including those receiving OMT,⁴⁹ still have a high risk of transmitting HCV.^{15 50} DCR can therefore be an addition to existing HCV prevention tools by engaging difficult-to-engage PWID in OMT and safer injection practices.

Although there are differences between the French and Vancouver contexts in terms of black market substance abuse (see above), and despite some heterogeneity

across and within the four different metropolitan areas where our study is being conducted,⁷ similarities between the two contexts exist, specifically regarding reduced access to sterile syringes, low socio-economic levels and a high proportion of PWID injecting in public spaces.^{7,42} COSINUS will help us understand the dynamic of HIV-HCV risk practices at a national level, both in already existing DCR and in sites providing other HR services. In France, incidence of fatal overdoses among PWID is low, making it difficult to reduce it significantly over a 12-month period. This could be related to the national harm reduction policy implemented in the 1990s including access to OMT⁶ and a high level of OMT coverage.^{7,46}

Many prospective studies have tested, evaluated and validated DCR worldwide and have shown several benefits for public health.²⁰ Although public opinion on DCR is mixed and has seen shifting attitudes over time,^{24,51} DCR acceptance by drug users and the drug-using community has been positive to date.^{52–55} Any evaluation of DCR needs to take into account the social environment where DCR are implemented, especially social acceptability by the neighbourhood.⁵⁶ DCR facilitate access to needles and provide safer places for users at high risk both to themselves and to their environment.^{41,57,58} They provide hygienic and safe conditions for intravenous users and staff. They reduce morbidity and mortality associated with overdoses and with HIV and HCV infections, which is not only beneficial to PWID but increases healthcare cost-effectiveness.⁵⁹ They promote access to opioid dependence treatment⁶⁰ and to prevention interventions related to drug injecting practices.^{61,62} However, few existing DCR provide education programmes for safer injection⁶³ or have a space to inhale drugs. Moreover, data about the combined effect of DCR with other HR services are sparse. The Canadian experience has shown the importance of the evaluation process of such a controversial HR tool.^{64,65} More specifically, evidence-based findings from an evaluation process of the DCR 'Insite' helped to advocate against its closure, which was threatened by the federal government.⁶⁶ The COSINUS cohort study will not only study the impact of regularly attendance in DCR on HIV-HCV risk practices in PWID in France, but will also assess the combined effect of DCR together with other HR services (eg, education about safer injection, access to OMT, social activities) on these practices.

Some limitations have to be acknowledged. First, all the data collected were self-reported. Although the use of self-reports may be subject to social desirability bias, studies have shown their reliability in drug-using populations.^{67,68} To control any such bias, we used trained interviewers independent of the participating harm reduction facilities. In terms of the diversity of our sample, all the PWID were recruited through easily accessible harm reduction facilities that conduct outreach actions, and which constitute the main contact that the PWID population has with the healthcare system. Another limitation is that, due to cost limitations of our study, we enrolled

only French-speaking participants. Further studies are planned to better investigate the impact of DCRs in all the population of PWID including non-French-speaking PWID that represent around 20% of people who attend DCRs.⁶⁹

In addition to evaluating DCR and other HR services, this cohort will be used for a more global assessment of the needs of the PWID population in terms of access to treatment for addictive disorders. It will also examine the reasons for not seeking treatment, while identifying users who may benefit from it. It will help to provide a greater understanding of users' social conditions, practices, their access to prevention and treatment services and of the role of incarceration and violence in this population often excluded from the healthcare system.

ETHICS AND DISSEMINATION

All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. All participants in the survey gave their informed consent.

The results from this cohort will enable health authorities shape health and harm reduction policies according to PWID needs, as well as improve and create novel harm reduction and therapeutic interventions. All relevant results will be published in peer-reviewed international scientific journals and presented at conferences, nationally and internationally.

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3.2 Objectifs opérationnels

Chacun des objectifs a fait l'objet d'une étude particulière, présentée sous la forme de manuscrits soumis à publication.

PARTIE I : état de l'art : Revue de la littérature des études des critères diagnostiques du trouble de l'usage chez les participants de programmes de réduction des risques

Une revue de la littérature a été menée ayant pour objectifs de faire une analyse documentaire de l'état actuel des connaissances sur les caractéristiques diagnostiques de l'addiction et du *craving*, chez les usagers de substances recrutés dans les programmes de HR.

Manuscript 2: Diagnostic characteristics of addiction and *craving* among active substance users in Needle exchange programs and Supervised injection facilities: a review of the literature.

PARTIE II : Les critères diagnostiques DSM-5

Afin de déterminer la stabilité des 11 critères diagnostiques du DSM-5 en fonction du contexte de soin, une étude psychométrique des critères a été réalisée avec les sujets Tx et HR.

Les caractéristiques psychométriques des 11 critères diagnostiques du DSM-5 du trouble de l'usage de l'alcool, du cannabis, de la cocaïne, des opiacés et du tabac ont été examinées avec la méthode IRT au sein de personnes en contexte de traitement (Tx). Nous voulions compléter les données déjà existantes en portant une attention particulière au critère "craving".

Manuscript 3: Item Response Theory analyses of DSM-5 substance use disorder criteria in French outpatient addiction clinic participants. How much is *craving* special ?

Les deux populations HR et Tx ont été comparées sur leurs caractéristiques sociodémographiques, l'usage de substances, les diagnostics de trouble de l'usage, la prévalence de chacun des critères diagnostiques et la fréquence et l'intensité du *craving* en tant que phénomène dynamique.

Manuscript 4: Comparison of patient seeking treatment and active substance users in harm reduction settings on DSM-5 Substance Use Disorder diagnosis and *craving* frequency and intensity.

Afin de tester la stabilité psychométrique des critères diagnostiques en fonction du contexte de soin (HR vs Tx), des analyses IRT sur les sujets HR et Tx regroupés en un seul groupe d'usagers réguliers et actuels de substances ont été effectuées et le fonctionnement différentiel des critères et de l'ensemble a été testé selon le contexte de soin (DIF et DTF).

Manuscript 5: Are DSM-5 substance use disorder criteria influenced by user care settings? An Item Response Theory analyses approach.

PARTIE III : La valeur prédictive du *craving* sur l'usage

Afin de tester la stabilité de la valeur prédictive du *craving* sur l'usage, un groupe de sujets HR a été évalué selon la même procédure EMA que celle utilisée auprès d'un groupe de sujets Tx ayant permis de mettre en évidence le modèle « *Cues-Craving-Use* » en contexte de traitement (Serre, Fatseas et al. 2012, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2018).

Manuscript 6: Implication of *craving* and *cues* exposure in substance use among active substances users in Harm Reduction settings: An Ecological Momentary Assessment Study

METHODE GENERALE

1 Populations

1.1 COSINUS

Les critères d'inclusion des sujets inclus en CAARUD dans la cohorte COSINUS étaient les suivants (Auriacombe, Roux et al. 2019):

- Usagers réguliers, ayant injecté au moins une fois au cours du dernier mois, des substances illégales (héroïne, cocaïne/crack, amphétamines, ecstasy, ... excepté le cannabis) ou des médicaments (méthylphénidate, buprénorphine, benzodiazépines, sulfate de morphine, oxycodone ...)
- Âgés de plus de 18 ans
- Francophones
- Acceptant de participer à l'étude et ayant donné leur consentement éclairé.

1.2 ADDICTAQUI

Les sujets inclus dans la cohorte ADDICTAQUI devaient (Auriacombe Accessed september 2019):

- Présenter au moins un diagnostic d'addiction, c'est-à-dire à 1 objet d'addiction ou plus, selon les critères du DSM-IV ou DSM-5 (selon les années).
- Être en demande de prise en charge pour cette addiction dans un centre de soins spécialisés en Addictologie
- Être âgés de plus de 18 ans
- Accepter de participer à l'étude et ayant donné son consentement éclairé.

2 Procédure

2.1 Partie II : Analyses des critères diagnostiques, étude psychométrique

Cette étude est une étude observationnelle transversale basée sur des données des 2 cohortes. Les données des sujets issues de la cohorte ADDICTAQUI ont été extraites d'une base de données existante (2008-2019), et les données des sujets COSINUS ont été recueillies par moi-même durant la thèse (2016-2018). Les études ont reçu l'autorisation des comités d'éthique.

Les deux échantillons ont été évalués au moyen des mêmes instruments standardisés lors d'entretiens semi-structurés conduits par des attachés de recherche clinique formés, incluant la totalité ou une partie de l'Addiction Severity Index (ASI), du Mini Neuropsychiatric Interview (MINI) et de l'échelle de *craving*. Seuls les diagnostics de trouble de l'usage de

substance du MINI et l'usage actuel et passé des substances (ASI) ont été ajoutés au questionnaire initial pour les sujets de la cohorte COSINUS, afin de ne pas rendre l'entretien trop long.

Si le sujet déclarait un usage régulier, défini comme ayant consommé la substance au moins 2 fois par semaine pendant 12 mois dans le but de se « défoncer » ou changer son humeur, actuellement (12 derniers mois) ou dans le passé (vie entière), les critères diagnostiques du DSM-5 étaient explorés.

2.2 Partie III : valeur prédictive du *craving* sur l'usage, étude en vie quotidienne

Il s'agit d'une étude observationnelle transversale en vie quotidienne d'une durée de 14 jours. La méthode EMA (Ecological Momentary Assessment) permettait d'évaluer les sujets durant leurs activités de tous les jours, en leur proposant de répondre plusieurs fois par jour à des questionnaires, complétés sur tablettes tactiles. La procédure de cette étude était identique à celle précédemment utilisée chez des personnes en traitement (Serre, Fatseas et al. 2012, Fatseas, Serre et al. 2015).

Critères d'inclusion et de non-inclusion spécifiques à l'étude EMA

Les usagers recrutés au CAARUD devaient avoir un usage régulier actuel de substances tel que défini dans l'ASI : 2 fois par semaine sur les 30 derniers jours. Les autres critères d'inclusion étaient d'identifier au moins une substance posant un problème principal parmi les substances sédatives et les stimulants et de présenter les critères diagnostiques DSM-5 du trouble de l'usage pour la ou les substances problématiques. Les participants devaient utiliser la voie injectée et/ou fumée pour la consommation de la/les substance(s) posant problème (sédatives et/ou stimulants) au moins une fois dans les 30 derniers jours.

Les critères de non-inclusion étaient de présenter une pathologie ou un handicap incompatible avec la compréhension et l'utilisation de la méthode EMA (par exemple déficience cognitive grave, handicap visuel ou auditif important), ou une difficulté de lecture de la langue française.

Déroulement de l'étude

Le sujet était informé de façon claire et juste sur le protocole et il lui était demandé un consentement éclairé et écrit.

Les sujets étaient évalués en entretien individuel une première fois à l'inclusion (entretien de base) (Figure 7). Cet entretien de bilan comprend une évaluation par l'ASI, le MINI, et un dosage urinaire. Après vérification des critères d'inclusion à la partie EMA, les sujets étaient convoqués pour un entretien d'entraînement durant lequel une présentation détaillée du protocole en vie quotidienne était faite. Au cours de cet entretien, le questionnaire d'habitude de consommation était réalisé afin de déterminer les *cues* personnels de chaque individu qui étaient ensuite saisis dans le programme EMA du sujet. Une tablette tactile leur était remise après un entraînement à l'utilisation de la tablette durant laquelle l'ensemble des questions et propositions de réponses ont été passées en revue avec le sujet pour s'assurer de la bonne compréhension de chacun des items. Les sujets étaient ensuite évalués en vie quotidienne durant les 14 jours suivants, et devaient répondre à des questionnaires sur la tablette tactile, à raison de 4 questionnaires par jour. Dans le cas d'une stratégie d'évaluation basée sur le temps, les évaluations se présentent automatiquement et sont répétées dans le temps selon une fréquence définie préalablement. Cette stratégie est particulièrement intéressante dans l'étude de variables qui persistent dans le temps et va permettre de couvrir les variations de cette variable sur l'ensemble d'une journée. Les intervalles entre deux évaluations étaient randomisés au sein d'un intervalle de temps. Suite à ces 14 jours, les sujets étaient reçus pour un entretien de débriefing durant lequel un bilan de leur consommation et de leur utilisation de services médico-sociaux était réalisé.

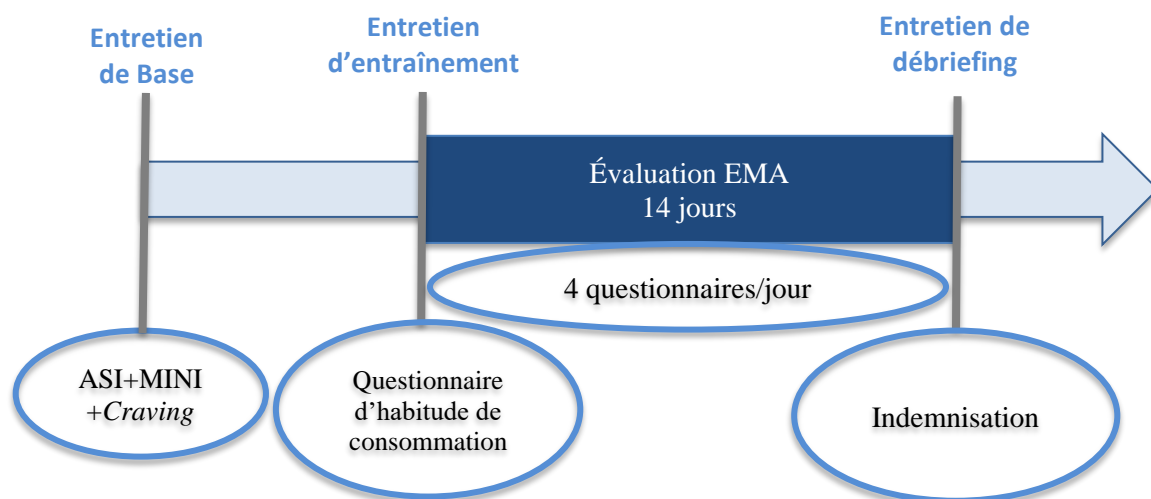


Figure 8: Schéma d'étude EMA

L'indemnisation en lien avec la participation à cette étude était versée au titre du remboursement des frais exposés. L'indemnisation était réalisée lors de la visite de fin d'études (entretien de débriefing). Seuls les individus ayant réalisé l'intégralité des 14 jours d'évaluations pouvaient être indemnisés en fonction du taux de réponse.

3 Outils

3.1 Mini International Neuropsychiatric Interview (MINI)

Le MINI est un hétéro-questionnaire permettant de diagnostiquer les troubles psychiatriques de l'axe I du DSM-IV, dont les addictions aux substances (Lecrubier, Sheehan et al. 1997). Deux périodes d'évaluations sont explorées : actuelle et passée. Dans ce projet nous avons utilisé une version du MINI adaptée aux changements introduits dans le DSM-5 pour le trouble de l'usage : regroupement des diagnostics d'abus et de dépendance du DSM-IV, ajout du *craving* comme critère diagnostique, et suppression du critère des problèmes légaux (American Psychiatric Association 2013). Le critère "*craving*" était exploré par la question : « Avez-vous éprouvé un désir fort et incontrôlable de consommer la substance ? ».

3.2 Addiction Severity Index (ASI)

C'est l'instrument le plus utilisé dans le monde pour l'évaluation d'un sujet usager de substances addictives (McLellan, Luborsky et al. 1985). Il recueille des renseignements dans sept domaines susceptibles d'être affectés par l'usage de substance ou un comportement addictif (état médical, emploi/ressources financières, substances – y compris alcool, tabac, comportements – comprenant le jeu, troubles des conduites alimentaires –, relations familiales et sociales, situation légale, état psychologique). De ces informations, sont générés par l'interviewer des scores pour chacun de ces domaines traduisant la sévérité du sujet évalué allant de 0 à 9. Un score de sévérité supérieur ou égal à 4 indique un besoin de prise en charge supplémentaire. La passation consiste en un entretien semi-structuré de 40 à 90 minutes par un évaluateur spécifiquement formé. La version de l'ASI utilisée a été adaptée pour prendre en compte la consommation de tabac et l'existence d'addictions comportementales comme le jeu et les troubles des conduites alimentaires (Auriacombe, Denis et al. 2004, Denis 2009, Denis, Fatséas F. et al. 2010). La fidélité test-retest à trois jours et la fidélité inter-cotateur sont très bonnes. Les scores de sévérité constituent une mesure valide de l'état du sujet pour chaque dimension considérée. La version modifiée de l'ASI (m-ASI) prenant en compte le tabac, les jeux d'argent ainsi que d'autres comportements sources de gratification (alimentation, jeux vidéo, etc.) a été utilisée dans ce projet (Denis, Fatseas et al. 2016).

3.3 Echelle d'évaluation du *craving*

L'échelle numérique d'évaluation du *craving* permet de mesurer la fréquence et l'intensité du *craving* sur les 30 derniers jours précédant l'entretien, pour toutes substances ou comportements utilisés de façon régulière par le sujet (Figure 8). L'intensité moyenne et

maximale sont explorées grâce à l'échelle numérique allant de 0 (pas de *craving*) à 10 (*craving* extrême). La définition du *craving* est explicitée au patient par l'évaluateur avant l'évaluation.

3.4 Questionnaire d'habitudes de consommation

Cet hétéro-questionnaire a été spécialement conçu pour l'étude EMA afin de déterminer pour chaque sujet les stimuli ou *cues* standards associés à son usage de la substance posant le problème principal, ainsi que les *cues* individuels (qui lui sont propres) susceptibles de déclencher le *craving* ou l'usage. La première partie de cet entretien permet d'explorer les consommations habituelles du sujet selon quatre caractéristiques : le lieu, l'entourage, le moment ainsi que le matériel utilisé. Pour chaque caractéristique, le sujet doit choisir les propositions qui correspondent le mieux à sa consommation habituelle à partir d'une liste standard (correspondant à celle présentée lors de l'évaluation en vie quotidienne). Le sujet peut ensuite proposer d'autres contextes qui lui sont propres sans limites de nombre de propositions. La deuxième partie de l'entretien permet au sujet d'apprécier de façon subjective quels sont les facteurs qui lui donnent particulièrement envie de consommer cette substance. Cette question ouverte peut être appuyée par des exemples de l'évaluateur (lieu, objet, émotions, situations, mal-être).

3.5 Questionnaire EMA (d'évaluation en vie quotidienne)

Ces questionnaires électroniques en vie quotidienne ont été créés spécifiquement pour l'étude. Ils permettent d'évaluer la situation dans laquelle se trouve le sujet au moment où il répond : lieu, entourage social, activités, humeurs, etc. Les questionnaires évaluent également la période écoulée depuis le dernier questionnaire en vie quotidienne : consommation de différentes substances, envie de consommer (échelle de 1 (aucune envie) à 7 (envie extrême)), difficulté de résister à cette envie, les raisons des consommations (envie soudaine, besoin physique ...) les pratiques à risque liées à l'usage (partage et réutilisation de matériel d'injection, pour fumer et sniffer, fréquence des pratiques à risques), les événements marquants ainsi que le fait d'avoir été en contact avec des contextes associés à l'usage de la substance (correspondant aux réponses données au questionnaire d'habitudes de consommation). La prise de médicaments prescrits pour l'addiction, les symptômes de sevrage, ainsi que la confiance du sujet en sa capacité à rester abstinent sont également évalués. Lors de la première évaluation de la journée, des questions évaluent le sommeil et les consommations nocturnes. Le questionnaire du soir recueille la quantité consommée de chaque substance au cours de la journée. Les sujets sont classés selon l'effet de l'objet d'addiction : sédatifs (opiacés, benzodiazépines, hypnotiques), stimulants (cocaïne, amphétamines, méthylphénidate). Pour chaque groupe, un questionnaire spécifique a été créé afin de renseigner précisément le *craving* et les contextes associés à la consommation de la substance posant le problème principal.

4 Modèles statistiques

4.1 Partie II : Analyses psychométriques

4.1.1 Échantillon et sous-groupe

Pour ce projet de thèse, 1489 sujets ont été considérés comme des usagers réguliers actuels et inclus dans nos analyses (1359 Tx et 130 HR) lors des entretiens de Base des deux cohortes. Tous les usagers réguliers et actuels d'alcool, d'opiacés, de cocaïne, de tabac et de cannabis ont été inclus dans chacun des groupes de substances, de façon indépendante de l'objet d'addiction posant le problème principal. Cela permettait d'avoir une variabilité dans les sévérités de trouble de l'usage, car parmi les sujets rapportant une substance comme la plus problématique, la majorité a un trouble de l'usage sévère (Chung, Martin et al. 2012, Kiluk, Frankforter et al. 2018, Dacosta-Sanchez, Fernandez-Calderon et al. 2019). Le nombre d'usagers réguliers actuels de stimulants (hors cocaïne), sédatifs, inhalants et hallucinogènes était trop faible pour les analyses IRT et elles n'ont donc pas été testées.

Tableau 3: Usagers réguliers actuels de chacune des substances par contexte de soin.

	Tx	HR	Total
Alcool	787	89	876
Opiacés	131	102	233
Cocaïne	141	82	223
Cannabis	504	95	599
Tabac	1014	128	1142

4.1.2 Analyse psychométrique des critères diagnostiques du trouble de l'usage de substance

Pour les analyses IRT, la même méthode a été appliquée pour les manuscrits 3 et 5 (Tableau 3). Toutes les analyses ont été effectuées dans Mplus 8 et R studio (Muthen et Muthen 1998-2017) (R Core Team 2018).

Dimensionnalité

Pour évaluer la dimensionnalité du modèle, nous avons réalisé une analyse factorielle de confirmation à un facteur (11 critères du DSM-5) basée sur l'erreur quadratique moyenne d'approximation (RMSEA), l'indice d'ajustement comparatif (CFI) et l'indice de Tucker-Lewis (TLI) (Tableau 3).

L'analyse factorielle de confirmation (AFC ou *CFA for Confirmatory factor Analysis*) est une approche complexe qui permet de vérifier l'hypothèse selon laquelle les éléments sont associés à des facteurs spécifiques. Au vu de la quantité d'études sur l'unidimensionnalité des 11 critères diagnostiques, nous avons fait le choix de tester directement l'association des 11

critères à un seul facteur (Hasin, O'Brien et al. 2013, Serier, Venner et al. 2019). Le principe du CFA est de vérifier si le modèle théorique n'est pas différent du modèle observé. Afin de vérifier cette absence de différence, des indicateurs sont calculés afin de mesurer la qualité de l'ajustement entre le modèle théorique et le modèle observé. Le RMSEA (Root Mean Square Error of Approximation) permet d'évaluer les écarts normalisés entre la matrice observée et la matrice estimée. L'indice d'ajustement non normalisé (aussi appelé indice Tucker-Lewis (Tucker and Lewis 1973) et le CFI (Comparative Fit Index) sont des indicateurs qui sont basés sur l'écart au modèle d'indépendance. Ces indicateurs examinent la différence entre le χ^2 du modèle testé et le χ^2 du modèle théorique. Leur valeur peut varier théoriquement de 0 à 1. L'unidimensionnalité était confirmée lorsque le modèle d'analyse factorielle à un facteur montrait un ajustement adéquat du modèle par le $CFI \geq 0.95$, le $TLI \geq 0.95$ et le $RMSEA \leq 0.06$ (Hu et Bentler 1999). Pour l'interprétation des coefficients de saturation (*factor loading*) des critères sur le facteur à une dimension, on considère qu'une variable n'est associée à un facteur que si sa saturation dépasse 0,40 en valeur absolue (Shmulewitz, Keyes et al. 2011).

Modèle de la théorie de réponses aux items (IRT)

Après avoir testé l'unidimensionnalité, nous avons appliqué le modèle théorique de réponse aux items à 2 paramètres, aux 11 critères diagnostiques du trouble de l'usage DSM-5 (Tableau 3). Nous avons généré les courbes caractéristiques des critères (ICC) pour déterminer la difficulté estimée de chaque critère sur le trait latent sous-jacent. Le paramètre de difficulté correspondait à la valeur l'axe des x (sévérité du trait latent) pour laquelle la probabilité d'approuver le critère était de 0,5, et la discrimination correspondait à la pente de la courbe à ce point de sévérité du trait latent (Embretson and Reise 2000, Shmulewitz, Keyes et al. 2011, Hasin, Fenton et al. 2012).

Fonctionnement différentiel des items et Fonctionnement différentiel du Test (DIF and DTF)

Nous avons testé le fonctionnement différentiel des items (ou *Differential item functioning DIF*) selon plusieurs covariables en fonction des objectifs (Tableau 3). Pour l'objectif du manuscrit 3, les DIF ont été explorés pour : le sexe, l'âge, le trouble de l'humeur actuel et le trouble anxieux actuel. Pour l'objectif du manuscrit 5 les DIF ont été explorés pour le contexte de soin. Les analyses de fonctionnement différentiel des items ont été réalisées à l'aide de modèles d'équations structurelles à causes multiples et à indicateurs multiples (ou le *multiple indicator multiple cause MIMIC*) permettant l'examen des DIF uniformes¹ (Jones

¹ Il existe deux types de DIF : uniforme et non-uniforme. Il y a un DIF uniforme lorsque les difficultés d'un item diffèrent d'un groupe à l'autre comme étudié ici. Il y a un DIF non-uniforme lorsque le paramètre de discrimination d'un item diffère d'un groupe à l'autre.

2006, Teresi 2006, Woods, Oltmanns et al. 2009, Kline 2011). L'une des forces du modèle MIMIC réside dans sa capacité à examiner et à ajuster l'impact des DIF pendant les analyses, ainsi que dans sa capacité à examiner simultanément plusieurs variables du groupe (Teresi and Fleishman 2007). La taille relativement petite de l'échantillon de certains sous-groupes (femme, usager de HR) a également mené au choix de la modélisation MIMIC (Jones 2006, Woods, Oltmanns et al. 2009, Kline 2011). Chaque ensemble de critères a été modélisé comme une variable latente indiquée par les 11 critères et régressé sur les caractéristiques des participants selon plusieurs modèles. Le modèle MIMIC est un cas particulier de modélisation d'équations structurelles qui inclut les relations entre : (a) le facteur (trait latent) et les critères ; (b) les covariables (ex : genre) et le facteur; et (c) les covariables et les critères, appelés effets directs des critères, car ils indiquent les effets des covariables sur les critères qui ne sont pas influencés par le facteur (Figure 9) (Blanco, Rubio et al. 2014).

Un DIF était indiqué lorsqu'un critère montrait une association statistiquement significative avec une covariable, après avoir tenu compte de l'association avec le facteur (trait latent). Cette association indépendante (effet direct) a été indiquée par des indices de modification (IM) statistiquement significatifs, ce qui suggère que l'ajout de cette association au modèle améliorerait l'ajustement du modèle. Si le DIF était indiqué, nous avons déterminé quel groupe de participants présentait une prévalence plus élevée pour le critère à la moyenne du trait latent. Pour chaque covariable, les 11 critères ont été testés, et un ajustement de Bonferroni pour des comparaisons multiples a été appliqué, utilisant ainsi un seuil de IM de 8,1 correspondant à un test de chi-square avec un degré de liberté de 1 et une valeur de $p \leq 0.05/11 = .0045$ pour identifier qu'une covariable avait un effet direct sur le critère.

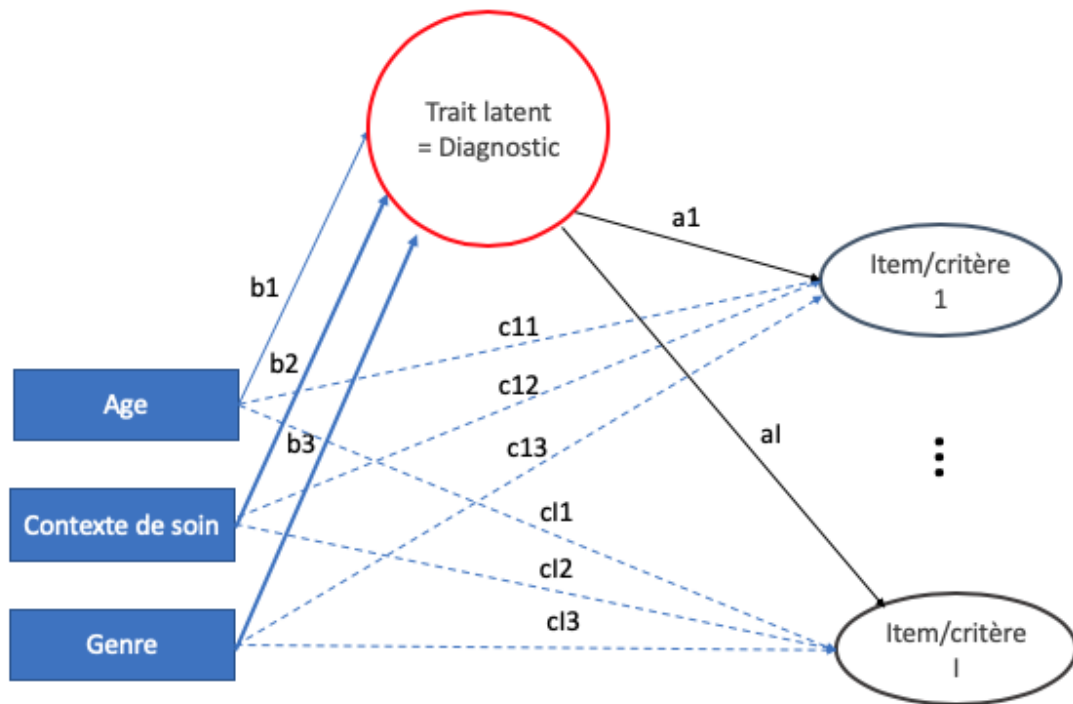


Figure 9: Exemple de modèle MIMIC.

Nous avons également examiné la différence de fonctionnement du test (DTF), pour vérifier si les critères établis dans leur ensemble (le " test ") fonctionnaient différemment par sous-groupe (Ex. HR vs Tx) (Tableau 3) (Raju, Van der Linden et al. 1995, Morales, Flowers et al. 2006). Nous avons utilisé le Rcode utilisé dans l'étude de *Shmulewitz, et al.* (Shmulewitz, Keyes et al. 2011) pour calculer la différence moyenne du nombre moyen de critères attendus pour les individus présentant la même sévérité de trait latent dans différents sous-groupes (Shmulewitz, Keyes et al. 2011). Une différence inférieure à 1 du nombre prévu de critères par sous-groupe indique qu'il n'y a pas de DTF, car des différences aussi faibles ne devraient pas mener à un diagnostic différentiel minimal du trouble de l'usage par sous-groupe (Shmulewitz, Keyes et al. 2011).

Information Totale

Des courbes d'information totale (ou *Total Information Curve =TIC*) ont été générées pour différents ensembles de critères afin de montrer leur capacité à discriminer les individus selon le spectre de difficulté des traits latents (Tableau 3) (Muthen and Muthen 1998-2017). Nous avons comparé quatre courbes pour chaque substance, représentant quatre ensembles de critères : les 7 critères de dépendance du DSM-IV, les 7 critères de dépendance du DSM-IV plus le critère "*craving*" (8 critères), les critères DSM-5 sans (10 critères) et avec le "*craving*" (11 critères). Le résumé de l'information totale globale fournie par chaque ensemble de critères a été indiqué par l'indice de zone d'information totale (ou *Total Information Area =TIA*)

(Tableau 3) (De Ayala 2009). Les intervalles de confiance (CI) des TIA ont été calculés à l'aide de la méthode bootstrap (Rcode disponible sur <http://www.columbia.edu/~mmw2177/IRT/bootirtinfo.txt>) (Shmulewitz, Keyes et al. 2011). Cinq cents échantillons bootstrap (ré-échantillons des données observées avec remplacement) ont été prélevés et la TIA a été calculée à partir des paramètres estimés de l'IRT dans chaque échantillon (R Core Team 2018). Les percentiles 2,5 et 97,5 de la distribution bootstrap du TIA indiquent l'intervalle de confiance (IC) à 95 % pour la TIA. Les CI à 95 % qui ne se chevauchent pas indiquent que l'ajout d'un plus grand nombre de critères a fourni beaucoup plus d'informations.

Tableau 4: Définition des termes statistiques clés (issue et adapté de Shmulewitz et al. 2011)

Terme	Définition	Utilisation dans ces analyses
Item	Une variable observable pour chaque répondant : ici les critères diagnostiques	11 critères diagnostiques alcool, cannabis, opiacés, cocaïne et tabac
Trait latent	Construction qui n'est pas directement observable, mais qui peut être déduite d'un modèle de relations entre les variables observées	Trouble de l'usage d'alcool, de cannabis, d'opiacés, de cocaïne et de tabac, déduite des relations observées entre les 11 critères
Dimensionnalité	Nombre de traits latent mesurés par un groupe d'items. La dimensionnalité est mesurée par les analyses de facteur. Un set d'items mesurant un seul trait latent est unidimensionnel	Confirmation que les 11 critères diagnostiques d'alcool, de cannabis, d'opiacés, de cocaïne et de tabac mesure une seule dimension (trouble de l'usage)
Analyses de Facteur (FA)	L'analyse de facteur examine la relation entre chaque item et les variables latentes sous-jacentes (appelées saturations ou <i>factors loading</i>) et détermine dans quelle mesure le modèle correspond aux données	Pour le trouble de l'usage, nous testons uniquement le facteur à une dimension, et utilisons les indices d'ajustement du modèle pour confirmer l'unidimensionnalité déjà rapportée par de nombreuses études
Indices d'ajustement du modèle	Différents indices quantifient l'ajustement du modèle. Il s'agit notamment d'indices d'ajustement comparatifs (p. ex. CFI, TLI), qui quantifient l'ajustement du modèle hypothétique au modèle nul (aucune relation entre les items), et d'indices d'ajustement absolu, comme l'erreur quadratique moyenne d'approximation (RMSEA)	Pour les critères diagnostiques, les modèles à un facteur ont donné lieu à des indices d'ajustement du modèle indiquant un bon ajustement du modèle
Théorie de Réponses aux Items (IRT)	Pour les ensembles d'items unidimensionnels, l'analyse de l'IRT estime la probabilité d'endosser chaque item le long du continuum des variables latentes en fonction de deux paramètres, la difficulté et la discrimination	L'analyse IRT sert à en apprendre davantage sur les critères diagnostiques proposés pour le DSM-5 et plus particulièrement la place du <i>craving</i> par rapport au trait latent et aux autres critères
Courbes caractéristiques des Items (ICC)	Les ICC représentent visuellement la probabilité d'approuver chaque item (axe des y) dans le continuum de sévérité des variables latentes (axe des x)	La figure 6 montre un exemple des ICCs pour les 11 critères du trouble de l'usage Sur l'axe des abscisses, le côté gauche est léger et le côté droit est sévère.
Difficulté	La difficulté représente l'emplacement le long du continuum du trait latent sous-jacent (axe des x) où l'item a une probabilité de 50 % d'être approuvé (axe des y). Un élément rare indique un caractère plus difficile, car seuls ceux qui ont un trait sévère manifesteront un item rare.	Les répondants ayant toutes les valeurs de sévérité du trouble de l'usage manifesteront des critères de difficulté légère (prévalence élevée), tandis que seuls les répondants ayant un trouble de l'usage sévère manifesteront des critères de difficulté élevée (faible prévalence)
Discrimination	La discrimination, c'est-à-dire la pente de la CCI en fonction de la difficulté de l'item, montre comment la probabilité d'approuver un item change dans le continuum de la sévérité. L'information de l'item est directement proportionnelle à la discrimination ; les pentes plus raides indiquent une information plus élevée tandis que les pentes plus plates indiquent une information plus faible.	Lorsque les personnes interrogées approuvent des critères très discriminants, des informations sont fournies sur la sévérité du trouble de l'usage, étant donné qu'il existe une fourchette spécifique de sévérité du trouble de l'usage à laquelle cet élément est susceptible d'être approuvé. Le fait d'approuver des critères à faible discrimination ne fournit pas cette information puisque la probabilité d'endossement de l'item est similaire selon la sévérité du trouble de l'usage.
Courbes d'information totale (TIC)	Une TIC montre comment l'ensemble d'items mesure le trait sous-jacent à chaque valeur le long du continuum de sévérité. Une TIC " plate " indique une information égale pour toutes les sévérités ; une TIC " à pic " indique plus d'information sur le trait latent à une sévérité spécifique	Permet de comparer quatre courbes représentant quatre ensembles de critères : les 7 critères de dépendance du DSM-IV, les 7 critères de dépendance du DSM-IV plus le critère " <i>craving</i> ", les critères DSM-5 sans (10 critères) et avec le <i>craving</i> (11 critères)
Indice de zone d'information totale (TIA)	L'information totale fournie par l'item est répartie sur l'ensemble du continuum du trait latent. Les TIA de différents ensembles d'items peuvent être testées pour indiquer si la quantité totale d'information dans un ensemble d'items diffère d'un autre	Correspond à la zone sous la TIC égale à l'addition des estimations des paramètres de discrimination des ensembles de critères respectifs. Les intervalles de confiance (CI) des TIA ont été calculés. Les CI à 95 % qui ne se chevauchent pas indique que l'ajout de critères a fourni plus d'information
Fonctionnement différentiel des items (DIF)	Un DIF indique que les paramètres de l'item (discrimination ou gravité) varient selon les sous-groupes de population. Idéalement, les éléments devraient fonctionner de la même façon dans tous les sous-groupes.	Les DIF ont été testés en fonction du contexte de soin, de l'âge, du genre, et des comorbidités psychiatriques pour les 11 critères diagnostiques du trouble de l'usage d'alcool, de cannabis, d'opiacés, de cocaïne et de tabac
Fonctionnement différentiel du Test (DTF)	La DTF se produit lorsque les répondants d'un sous-groupe de la population étudiée, au même degré de sévérité du trait latent, approuvent un nombre différent de critères au total. Le DTF pourrait conduire à un diagnostic différentiel en sous-groupes.	Les DTF ont été testés en fonction du contexte de soin, de l'âge, du genre, et des comorbidités psychiatriques pour les troubles de l'usage d'alcool, de cannabis, d'opiacés, de cocaïne et de tabac

4.2 Partie III : analyses HLM

Dans un premier temps, nous avons décrit les sujets sur l'ensemble des variables recueillies. La méthode EMA permet d'examiner des variations intra-individuelles, et de décrire l'évolution d'une variable au cours du temps. L'analyse des variations interindividuelles permet de caractériser les différences individuelles. Dans ce cas, une moyenne est réalisée à partir des données répétées, cette méthode donnant une meilleure estimation qu'une simple donnée ponctuelle. Enfin, la méthode EMA permet de mettre en évidence des relations temporelles entre plusieurs variables, et notamment un lien prospectif entre une variable rapportée à un temps T0, et une autre variable rapportée à T+1.

L'association au sein d'une même journée entre le nombre de *cues*, l'intensité du *craving* et l'usage de substances a été analysée en utilisant la modélisation hiérarchique linéaire et non linéaire dans HLM, version 6.03 (Raudenbush, Bryk et al. 2005). La relation entre les *cues*, le *craving* et l'usage de substance a d'abord été examinée dans le cadre d'études transversales, suivies d'analyses décalées dans le temps où le nombre de *cues*, de *craving* ou d'usage de substances à une évaluation donnée (T0) a prédit l'intensité du *craving* ou de l'usage (*outcome*) les évaluations suivantes (T1). Des modèles linéaires multi-niveaux ont été utilisés pour la mesure continue (*craving*, nombre de *cues*), et des modèles de Bernoulli ont été utilisés pour les modèles dichotomiques (usage de substance). Toutes les analyses ont été ajustées pour tenir compte des effets de l'âge et du sexe d'une part et de l'*outcome* à T0 d'autre part.

Le modèle général utilisé est illustré comme suit :

$$\text{Usage de substance}_{ij} = \beta_{0j} + \beta_{1j}\text{Craving}_{ij} + r_{ij}$$

où β_{0j} représente le score d'usage de substances attendu pour la personne j quand le score de *craving* est zéro, $\beta_{1j}\text{Craving}_{ij}$ représente le changement attendu du score d'usage de substances pour la personne j en fonction du *craving* précédant, et r_{ij} est le risque d'erreur associé à l'observation i pour la personne j . Au niveau des observations, les intersections et les pentes seront ensuite modélisées au niveau de la personne en utilisant les équations suivantes :

$$\beta_{0j} = \gamma_{00} + \gamma_{01}\text{Sexe}_j + \gamma_{02}\text{Age} + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + \gamma_{11}\text{Sexe}_j + \gamma_{12}\text{Age} + u_{1j}$$

où γ_{00} est l'intersection globale et γ_{01} , γ_{02} , sont les effets principaux du sexe, de l'âge; γ_{10} est l'effet principal sur le *craving* et γ_{11} , γ_{12} sont les termes d'interaction multi-niveaux pour le sexe, l'âge concernant l'association entre *craving* et usage de substance.

Le risque d'erreur alpha sera fixé à 5 % pour tous les tests.

Une analyse de puissance statistique réalisée sur des données d'une précédente étude utilisant la méthode EMA en milieu clinique (Serre, Fatseas et al. 2012, Fatseas, Serre et al.

2015), a permis de calculer que pour la détection d'une taille d'effet petit à moyen ($R^2 = 10\%$), un total de 40 participants serait nécessaire (basé sur une analyse de régression linéaire avec onze prédictors, notamment l'âge, le sexe, l'éducation, la présence de comorbidités psychiatriques). En s'attendant à une compliance minimale obtenue pour 68% des participants (Mackesy-Amiti and Boodram 2018), un échantillon total de 53 personnes sera recruté pour permettre le taux de compliance prévue.

RESULTATS

PARTIE I : état de l'art : Revue de la littérature des critères diagnostique du trouble de l'usage chez les participants de programme de réduction des risques

Manuscript 2: Diagnostic characteristics of addiction and craving among individuals in Harm Reduction Programs: a review of the literature.

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Author contributions

Study conception and design: CK, MA, J-PD. Selection and critical review of studies: CK, FS, CD, SM, MA. Drafted the first version of the manuscript: CK, FS, CD. All authors significantly contributed to the manuscript and approved the final version.

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Abstract

Background: To describe the state of current knowledge on the diagnostic characteristics of addiction and craving, among individuals who use substances recruited in Harm Reduction programs (HRP) and to examine how these factors related to excessive and problematic use and risk.

Methods: This review is an examination of the literature. Relevant literature was selected from online PubMed and PsycInfo database up to January 5, 2019. We considered all studies that included individuals who use substances in HRP and assessed information on diagnostic characteristics of addiction, or craving.

Results: Among the 190 articles retrieved, 11 met criteria for inclusion: 3 examined craving and 8 use disorder diagnostics. All individuals met criteria for opiate use disorder, 68% for alcohol and 79% for cocaine use disorders. Among study selected participants, 57.4% rated craving as moderate or severe and 2 studies suggested an association between craving and HIV risk practices. The overall quality of studies was low, due to lack of details on diagnostic criteria and lack of prospective studies to better assess the link between craving and HIV risk practices.

Conclusions: Among individuals who actively use substances recruited in HRP, prevalence of substance use disorders was high and craving could have an impact on some persistent risk behaviors. Prospective studies are needed.

Keywords: Substance Use Disorder prevalence; Substance use Disorder criteria; Craving; HIV risk practices; Needle Exchange Program; Supervised Injection Facilities.

INTRODUCTION

Addiction or substance use disorder is characterized by loss of control of use, relapse, and craving.¹⁻³ Many studies, including those that have examined the validity of substance use disorder diagnostic criteria, highlighted the predictive value of craving over substance use.⁴⁻⁸ However, most of these studies recruited individuals who use substances in treatment settings or attempting to access treatment or in an environment that makes use difficult.^{2,3} Hence, it is possible that some of the diagnostic criteria and craving could be induced by treatment seeking behavior.⁹ It therefore is of interest to determine how these diagnostic characteristics of addiction are endorsed in individuals who actively use substances in an environment that is substance-use-friendly as harm reduction programs. Participants of harm reduction programs have significant probability of having a substance use disorder, are actively engaged in use and they are accessible to research. Harm reduction of substance use identifies the immediate negative health, social and legal consequences of substance use as the target for intervention rather than substance use or the substance use disorder itself.¹⁰⁻¹³ Harm reduction programs such as Needle Exchange Programs (NEP) and Supervised Injection Facilities (SIF), were adopted in many countries to face the HIV epidemic among people who inject drugs (PWID).¹⁴ To access such programs no abstinence or reduced use is needed.¹⁰⁻¹² Despite the positive impact of such programs, and the demonstration that they reduce at risk behavior and seroprevalence,^{15,16} studies have also shown that some risk behavior persist among some individuals who actively use substances accessing NEP.^{17,18} Comorbid psychopathology was a possible factor limiting positive impact of NEP, because among PWID in medication-assisted treatment with methadone, comorbid psychopathology was significantly associated with HIV-transmission-risk behaviors, but the characteristics of the addictive disorder has not been explored as a possible other limitation factor.^{19,20} Individuals who access harm reduction programs are well documented as a group with excessive and problematic use of several substances, many risk-practices and vulnerabilities, but to which extent their use is driven by addiction, craving, or other potential causalities remains to be studied. The objectives of this review of the literature were 1) to describe the state of current knowledge on the diagnostic characteristics of addiction and craving for alcohol, tobacco and illegal substances, among individuals who actively use substances recruited in Harm Reduction programs, an environment that is substance-use-friendly and 2) to examine how diagnostic characteristics of addiction and craving may relate to excessive and problematic use and risk behavior.

METHOD

This review is an examination of the literature based on the Cochrane Collaboration method.²¹ We followed the recommendations from the Preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) statement and PICOS regarding reporting items that we considered applicable to this review.²² This paper is a qualitative review of the existing literature and was not aimed to evaluate specific interventions nor to compare interventions (Appendix 2: PICOS criteria for inclusion of primary articles).

a) *Study eligibility criteria*

Inclusion criteria for selecting studies were: (a) the population must be persons who actively use substances recruited in NEP or SIF; (b) data should be available to define the prevalence of substance use disorder or abuse or dependence diagnoses or individual diagnostic criteria prevalence, or craving. For diagnosis and diagnostics criteria, all editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Disease (ICD) nomenclatures were considered. We excluded studies based on inappropriate study population, recruitment sites/methods, or lack of available information on diagnostic characteristics of addiction, or craving. Language was not a restrictive selection criterion.

b) *Search method, selection of studies and quality assessment*

Data sources and search method

The relevant literature was selected from online PubMed and PsycINFO databases up to January 5, 2019 via EBSCOhost. The search strategy and terms for Supervised injection facilities were based on the work of Potier et al¹⁶ in their systematic review on SIF-induced benefits and harm. For craving, we expanded our search to include other wording such as “urge to use” and “desire to use”. Although there was slight variation in the specific search format between databases, the following search terms and combinations were used: (supervised injection facilities OR Needle-Exchange Programs) AND (((Substance-Related Disorders diagnosis OR Mental Disorders diagnosis OR drug abuse diagnosis OR drug dependence diagnosis) OR (Motivation OR Drug-Seeking Behavior OR Craving OR urge OR desire)). Appendix 1 (supplementary material) displays the detailed search for PubMed and PsycINFO databases. We hand-searched the references listings of publications obtained with this electronic search to obtain additional publications. All studies identified during the search were stored in EndNote® version X8.²³

Study selection

Duplicate studies were searched by using the “Find Duplicates” tool in EndNote® X8 and by manual examination.²³ After removal of duplicate studies, abstracts of all studies were reviewed and publications including current individuals who use substances recruited in NEP

or SIF (exclusively or not) were selected. If the recruitment method was not specified in the abstract and participants were individuals who use substances the study was selected. The full texts of primary articles identified were retrieved and assessed against the PICOS criteria applicable to this review (Appendix 2: PICOS criteria for inclusion of primary articles). Studies that met all of the inclusion criteria were selected. Even if declared aim was not focused on exploring substance use disorder diagnosis or craving, the methods and data analysis sections were screened to identify any diagnosis or craving measures. Reasons for exclusion from further review were coded as one or more of the following: (a) inappropriate population (not individuals with problematic substances use); (b) inappropriate recruitment sites/methods (subjects recruited in hospitals or addiction treatment centers, or recruited for treatment access outside NEP sites, mixed samples, internet or snowball methods); (c) Treatment recommendation or case studies; (d) reviews of the literature and meta-analyses; (e) lack of information on diagnostic characteristics of addiction, or craving.

Quality assessment

Articles meeting the selection criteria were quality assessed using a standardized critical appraisal based on 4 levels of quality in relation to our objective (Appendix 3). Level a: documentation of absence of current active addiction treatment access. The explicit assessment of current treatment received was considered as high quality and its absence as low quality. Level b: availability of individual diagnostic criteria. If available this was considered as high quality and if not as low quality. Level c: craving assessment. If there was an explicit definition of craving and use of a quantitative scale this was considered as high quality. Level d: Methods used to assess the link between diagnostic characteristics of addiction/craving and excessive and problematic use and risk behavior. The identification of a prospective link was considered as the best quality of evidence, a significant association at a given time was estimated as moderate quality and a link based on retrospective reporting as low quality.

c) Data extraction

We used a standardized form to extract the following variables from the included studies: a) Study characteristics (author, journal, year of publication, type of study (e.g., cross-sectional, longitudinal, cohort, retrospective), inclusion and exclusion criteria, use of DSM or ICD criteria for Substance Use Disorder (SUD) or tools (scale, item) for craving measures and type of analyses (retrospective, cross-sectional or prospective)); b) Participant characteristics (sample size, age, substances used, addiction treatment); c) outcome characteristics: SUD diagnosis (prevalence of SUD for each substance, poly-addiction and diagnostics criteria), craving (prevalence, frequency and intensity), and d) Link between diagnostic

characteristics/craving and excessive/ problematic use (use frequency and quantity, severity of damages (medical, social, financial)), or risk behavior, (HIV/HCV risk behavior (injection, needle sharing, etc.)). Two independent reviewers trained in systematic searches screened studies, and a third reviewer resolved discrepancies. We reported sample overlapping (five studies) in order to avoid overestimation of redundant results.

RESULTS

a) Search results

The online PubMed and PsycINFO search resulted in 189 articles and a hand search resulted in 5 additional articles, resulting in a total of 194 articles. Four were excluded because they were duplicate studies. Based on titles and abstracts, 99 articles were considered of interest and obtained as full text. Based on full text, 11 articles met all inclusion criteria (**Figure 1**). These studies were published between 1997 and 2011 Relevant studies were described separately and presented in chronological order in **Table 1** (substance use disorder prevalence and diagnostic criteria) and **Table 2** (craving). Three studies examined craving, 8 studies examined the diagnosis of substance use disorder, and none examined both of these variables.

[Insert Figure 1]

b) Characteristics of the studies and samples

Of the 11 articles, 4 were cross-sectional and 5 were cohort studies. Among the 11 studies included in this review, 6 were from the United State, 3 from Australia, 1 from the United State and Australia and 1 from China. For all the studies, subjects were recruited in NEP. There were two types of NEP in these studies, fixe and mobile. There was no study that assessed the prevalence of SUD or craving in SIF participants.

Six studies out of 11 qualified as high quality. For 4 studies addiction treatment was an exclusion criterion. One study excluded subjects who had received formal substance abuse treatment over the previous 6 months,²⁴ and another study subjects who had received treatment for heroin in the last month ²⁵. Two studies included subjects without current substance use disorder or psychiatric treatment with no time specification.^{26,27} Three studies explored the prevalence of subjects who received current or lifetime addiction treatment.^{26,28,29} Three studies had no explicit information about the treatment engagement of subjects included.

The 11 studies reported a total of 2,121 participants and the average sample size was 192.8 (SD 119, median 162, range 80-422). Three studies recruited subjects in the Baltimore Needle Exchange Program (BNEP), which operates in a mobile van that travels to different sites and had recruited a large sample of persons with opioid addiction between November 1999

and July 2002. All participants of this cohort were administered a comprehensive assessment battery including the structured Clinical Interview for the DSM-IV (SCID-I) for the diagnosis of opioid dependence. We considered that the same subjects were included in these 3 studies.²⁶⁻²⁸ The analysis of two studies were based on the same sample of 103 PWID, with current SUD assessed with the Mini International Neuropsychiatric Interview (DSM-IV diagnosis), accessing a NEP in Melbourne, Australia, between February and July 2004.^{30,31} Overall, we estimated that the 11 selected studies, reported data from 1,378 different individuals who actively use substances recruited in NEP (NEP participants).

c) Characteristics of subjects

Ten studies included participants with a minimum age of 16 or 18 years, and one study assessed young adults aged between 16 and 24 years.³² In all studies, the majority of subjects were males (range from 60% to 72.8%). Two studies compared NEP participants with patients in treatment or seeking-treatment for addiction,^{24,25} and one compared NEP participants with PWID not in NEP.³²

d) Diagnostic characteristics of addiction (Table 1 and 2)

Diagnostic Tools

Five studies used the Structured Clinical Interview for DSM Disorder (SCID),^{24,26-28,33} one the Composite International Diagnostic Interview for DSM (CIDI),²⁵ and two the Mini International Neuropsychiatric interview (MINI) (Table 1).^{30,31}

Prevalence of SUD

Among the 8 studies that assessed Use Disorder diagnoses, only one had a moderate diagnostic quality because it assessed the mean number of criteria endorsed in the NEP participants.²⁵ The other studies assessed only the prevalence of subjects with or without a SUD diagnosis. However, among them there was differences in information quantity, some studies explored more substances than others or more details in the diagnosis such as differentiating Dependence from Abuse diagnoses and current from lifetime (Table 2).

Among the eight studies assessing the prevalence of SUD, 5 explored only opiate or alcohol use disorders,^{24,25,30,31} and 3 performed a systematic evaluation for several substances.²⁶⁻²⁸

Among studies that assessed SUD (Table 1), 100% of individuals met criteria for opioid dependence. The second highest prevalence was current and lifetime cocaine use disorder with a prevalence of 68% and ranged from 78% to 79% respectively.²⁶⁻²⁸ Alcohol use disorder was the third most endorsed substance with a current and lifetime prevalence ranging from 25% to

70% and from 68% to 69% respectively,^{24,26,27,30,31,33} followed by cannabis use disorder with a current and lifetime prevalence of 8% and 51% respectively.^{27,28} Current and lifetime sedative use disorder prevalence was 4%,²⁸ and ranged from 20% to 23% respectively.²⁶⁻²⁸ Current prevalence of stimulant use disorder (except cocaine) was 0%, and lifetime prevalence 11%.²⁸ Hallucinogen use disorder had a current prevalence of 0.9% and lifetime prevalence of 13%.²⁸ Studies that compared NEP participants with patients in treatment or seeking-treatment in Methadone Medication-Assisted Treatment (MMAT) showed that NEP participants had higher rates of alcohol abuse/dependence (30%) than MMAT patients (19%).²⁴ One study showed that cocaine dependence was significantly associated to HIV risk behavior assessed by the Risk Assessment Battery (RAB).²⁷

Prevalence of poly-substance addiction

One study reported an average of 3.3 lifetime SUDs and 1.3 current SUDs in addition to opioid dependence.²⁸ The two other studies reported that in their sample of NEP participants, 25.2% had an alcohol use disorder in addition to the primary SUD.^{30,31}

Diagnostic criteria for substance use disorders

Only one study reported on the distribution of SUD diagnostic criteria (DSM-IV dependence) among NEP participants. However, the paper reported only the average number of endorsed criteria and not which specific criteria were met. The mean number of use disorder criteria endorsed by the total sample was 5.5 (range 1-7), with significant differences ($p < 0.005$) between the NEP group (mean=5.1) which endorsed fewer criteria than the medication-assisted treatment (5.5, $p < 0.05$), detoxification (5.6, $p < 0.01$) and residential rehabilitation (5.7, $p < 0.005$) groups.²⁵

Craving

Three studies examined craving among NEP participants (Table 2). The quality level of craving assessment was low. Only one study had a clear definition of craving³⁴. Considering the level of assessment, two studies supported the existence of craving in this NEP population, and one assessed craving intensity with a 4-point category scale (not at all, slight, moderate and severe) considered as moderate quality.²⁹ Craving was reported by more than half of the participants.²⁹ No study explored the intensity of craving with a Visual Analogical Scale.

Link between diagnostic characteristics/craving and excessive/problematic use or risk behavior

Three studies assessed the link between diagnostic characteristics of addiction or craving and excessive and problematic use and risk behavior. One study had a moderate level of quality because it showed a significant cross-sectional association between cocaine diagnosis/craving and HIV risk behavior,²⁷ and two a low quality because the link was based on retrospective reports.^{32,34}

Craving was associated with at-risk practices. The probability of sharing in any given situation increased as craving increased.³⁴

DISCUSSION

The objectives of this literature review were to describe the current knowledge on the diagnostic characteristics of addiction and craving, among individuals who actively use substances recruited in Harm Reduction programs, and to examine how the diagnostic characteristics of addiction and craving related to excessive and problematic use and risk behavior.

Our literature search retrieved 11 papers from an initial of 189. After controlling for duplicates, we determined they reported a total of 1,378 persons who actively used substances recruited from NEP in North-America, Australia and Asia. No studies assessed SUD criteria and craving in SIF. The studies were published between 1998 and 2011 and our research did not find studies published since then. Because HR interventions aim to reduce the harm that substances cause to individuals without reducing substance use or acting on substance use disorder characteristics it is not surprising that the question of the diagnosis of addiction was not extensively studied.^{10,11,13}

Only 8 studies examined use disorder diagnostic criteria and the overall quality of studies was low. Seven studies assessed only the prevalence of SUD without giving diagnostic criteria details. The prevalence of SUD was similar across the studies,^{24,26-28,30,31} indicating that among individuals who actively use substances in use-friendly context, use seems guided by addiction. Although no study used DSM-5 diagnostic criteria but used dependence and abuse diagnoses defined by the DSM-III and DSM-IV criteria, the findings supported that most of the individuals who reached the NEP facilities had loss of control of their substance use, and would more likely meet substance use disorder criteria.

None of the studies reported on the prevalence and distribution of each diagnostic criterion. Only one study gave the average number of endorsed DSM-IV dependence criteria reported by NEP participants,²⁵ and reported that NEP participants endorsed fewer criteria than individuals who received methadone and buprenorphine maintenance treatment, or in detoxification and residential rehabilitation.²⁵ First, these results highlight that diagnostic criteria were endorsed even in a context of active substance use support. The fewer criteria endorsed among NEP participants in comparison to treatment participants could be explained

by individuals in treatment being more likely to have reduced their substance use and thus more likely to experience more withdrawal symptoms or more opportunities to report more failure in quit attempts, and as a consequence to endorse more diagnostic criteria. Otherwise, it may be that individuals who actively use substances recruited in NEP have a less severe use disorder with less dependence symptoms (diagnostic criteria). But this hypothesis is in contrast with results showing that NEP participants have more a severe substance use profile than patients in treatment.^{25,35}

Few studies explored poly-dependence among individuals who actively use substances recruited in NEP. One study indicated the mean number of lifetime and current SUD in addition to opioid dependence,²⁸ and showed that poly-dependence was common in this population. Other studies among persons using opiates have shown that substance use comorbidity was associated with greater substance use and higher rates of at-risk behaviors,³⁶ despite being in substance addiction treatment. Another limitation was that among the 8 studies investigating the prevalence of SUD, 3 assessed persons using opioid (heroin) only. In these studies, all the subjects met criteria for opiate use disorder, based on DSM IV criteria.²⁶⁻²⁸ Another study gave a 98% prevalence of heroin use disorder in a sample lumping NEP participants and subjects recruited in agencies treating heroin addiction.²⁵ These studies excluded subjects who did not have opioid use disorder, thus, in these studies the prevalence of other SUD could not be determined. Another study had as additional inclusion criteria a minimum score of 8 with the Alcohol Use Disorder identification test (AUDIT) in addition to having injected heroin or cocaine in the past 30 days.³³ Only three studies did not have substance restrictions in their inclusion criteria and could therefore be the most representative of the prevalence of substances used. They reported that 100% of NEP participants had opiate use disorder and the prevalence of Alcohol use disorder ranged from 25.2% to 29.5%.^{24,30,31.}

One study assessed frequency and intensity of craving with a 4-point scale.²⁹ None of them explored the intensity of craving with a Visual Analogical Scale that is considered as one of the best methods to assess symptoms.³⁷ The intensity of perceived craving was leveled over the past 30 days. However craving is a dynamic phenomenon, it shows fluctuations through the day and is responsive to the environment, which makes it difficult to evaluate in retrospective reporting.^{4,38}

More than half of NEP participants reported moderate to severe craving.²⁹ The prevalence of NEP participants who did not perceive craving is unknown. Several reasons may explain why some individuals who actively use substances recruited in NEP, probably with SUD criteria, do not report craving. The first is that regular use may prevent the expression or perception of craving. Moreover, in the study evaluating craving,²⁹ the results were not

controlled according to use of opioid medicated-assisted treatments that reduce craving.³⁹ A limitation in the 3 studies that explored craving among NEP participants, was a lack of a clarified definition of craving and how it was explained to the participants.³⁸ It seems to be important to assess the diagnosis of SUD and craving together, with specific tools adapted to craving, to confirm that individuals who actively use substances recruited in NEP have SUD and better understand if craving is not present or not perceived by controlling potential exposure to craving reducing treatments.

Three studies, of moderate to low quality, explored the link between diagnostic characteristics of addiction or craving and risk behaviors. One study was rated as moderate level quality (cross-sectional link),²⁷ and two as low quality (retrospective report).^{32,34} Interestingly these studies suggested an implication of craving in at-risk practices and showed a significant association between cocaine dependence and HIV risk behavior.^{27,32,34} Thus, assessing and monitoring craving among individuals who actively use substances recruited in NEP may improve the efficiency of NEP by reduced risk of disease transmission. However harm reduction programs seem to impact indirectly this association because NEP participants felt more confident in their ability to resist to reuse or share injection equipment when they had craving or “high” than individuals using substances not attending NEP.³² These findings are consistent with previous research among PWID in treatment, reporting that craving was one of the most reported reasons for taking undue risks in sharing injection equipment.⁴⁰ Repeated assessment of craving in daily life could help to better assess prospectively the role of craving in substance use and risk behaviors in these individuals with problematic substance use.^{4,5} Finally, craving is very much linked to people's environment (cues/stimuli can depend on the network, consumption patterns, psychosocial characteristics of housing/employment, ...), so these data must also be taken into account to reduce problematic uses.^{5,41}

This review of SUD prevalence among individuals who actively use substances in HR programs has limitations that need to be acknowledged. A difficulty for selecting papers was to correctly characterize users. Our target population was individuals who actively use substances in an environment that is substance-use-friendly, outside of an abstinence-oriented context. This did not exclude that they could be attending treatment, but the inclusion and assessments were done while in an environment that is substance-use friendly. This excluded studies that focused on users outside of any type of support and those studies assessing users in a treatment center context. Another difficulty for selecting studies was that most were not primarily concerned with the evaluation of substance use disorders or craving.

The lack of data on SUD diagnostic criteria and craving characteristics among individuals who actively use substances recruited in NEP may be an important omission in efforts to enhance the individual and public health benefits of harm reduction programs. It also seems important to better characterize NEP users in order to improve this transition between harm reduction services and addiction treatment programs.

To conclude, in this review the diagnostic criteria and craving were highly prevalent among individuals who actively use substances in use-friendly environments such as NEP. However, few studies assessed craving, and study limitations make result interpretation difficult. Nonetheless, it seems that among NEP participants, craving could be associated with HIV and HCV risk practices, that highlights the possible need for considering craving in a comprehensive harm reduction effort. It will be important to confirm these findings in different samples and prospective studies are needed to better understand the role of craving in this specific group of users.⁴² The identification and management of craving and its associated factors in harm reduction programs during the distribution of sterile needle and drug paraphernalia could be considered to improve the efficiency of current harm reduction strategies.

Figure 1: Flow chart of research strategy and study selection

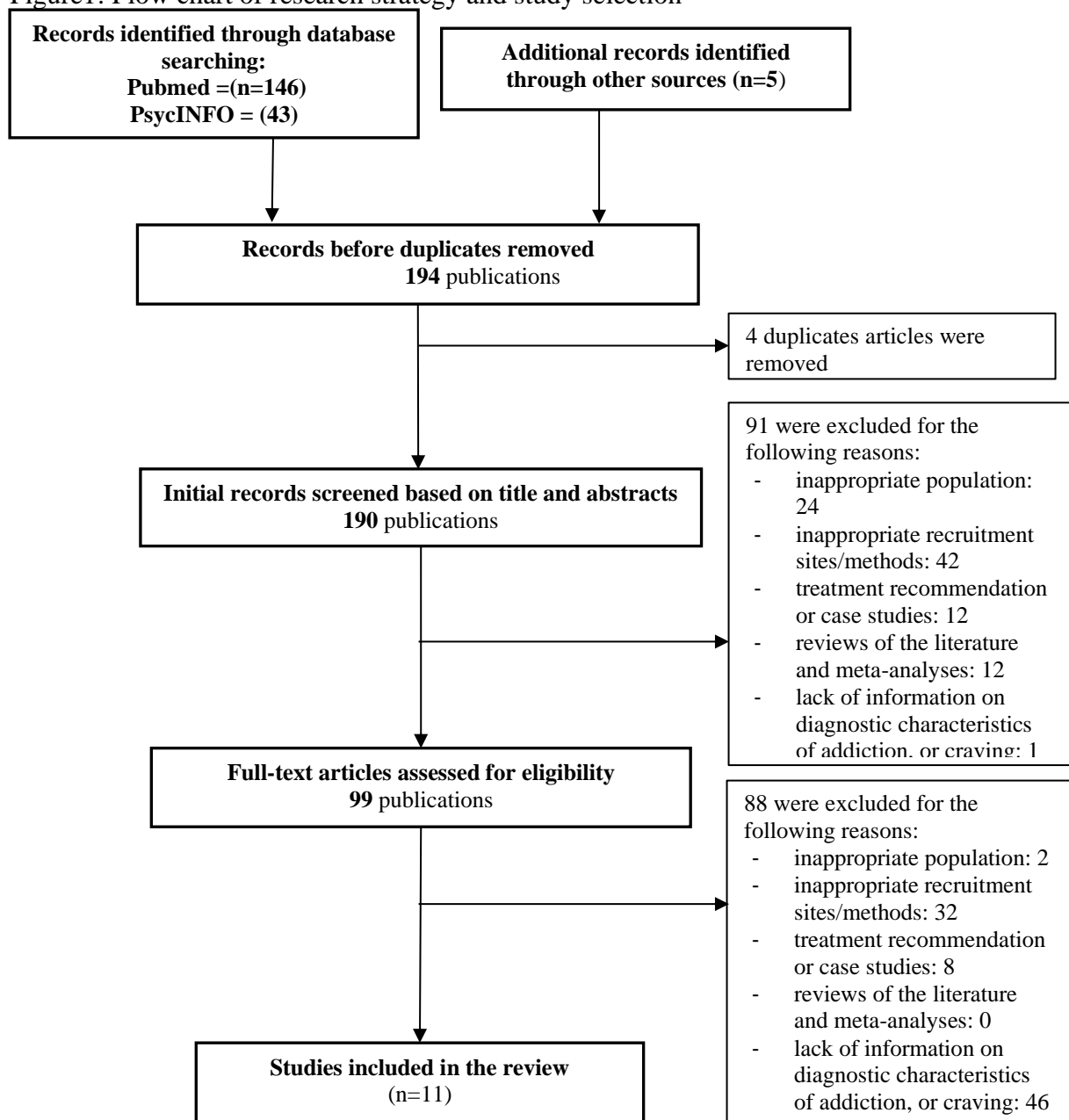


Table 1: Summary table of data from studies assessing substance use disorder prevalence and criteria

Study	SUBJECTS				METHODS	RESULTS		
	N	Substance	Inclusion criteria: Diagnosis / use	Recruitment site		Diagnosis measure	Diagnostic characteristics of addiction	Link between Diagnostic characteristics of addiction and excessive/ problematic use or risk behavior
Brienza et al., 2000	251	Heroin/cocaine	Not substance treatment in last six months	NEP	SCID DSM-III TR	29.5% alcohol dependence/abuse	-	a) low b) low
Stein, et al. 2002	187	Alcohol	PWID, injected heroin or cocaine, scored 8 at AUDIT	NEP	SCID DSM-IV	85% current alcohol abuse or dependence (80% for abuse, 70% for dependence)	-	a) low b) low
Ross et al., 2002	80	Heroin	Current heroin use Not in treatment	NEP	CIDI DSM-IV	100% current heroine dependence, mean criteria endorsed: 5.1.	-	a) low b) low
Kidorf et al., 2004	414	Opiates	Person with opioid dependence	NEP	SCID DSM-IV	Current dependence/abuse: 68%/5.3% cocaine, 33%/2.4% alcohol, 7.5%/<1% cannabis, 4.1%/1.7% sedative, 0%/<1% stimulant, <1%/0% hallucinogen, 3.1/1.9 other substances. Lifetime dependence/abuse: 78%/8.2% cocaine, 68%/8.5% alcohol, 51%/19.6% cannabis, 22%/12.8% sedative, 10.6%/6% stimulant, 12.8%/8.9% hallucinogen, 12.8%/7.7% other substances.	-	a) low b) low
Kidorf et al., 2005	302	Opiates	Person with opioid dependence	NEP	SCID DSM-IV	79% cocaine dependent, 22% sedative dependent, 69% alcohol dependent.	-	a) low b) low

Study	SUBJECTS				METHOD S Diagnosis measure	RESULTS		
	N	Substance	Inclusion criteria: Diagnosis / use	Recru itment site		Diagnostic characteristics of addiction	Diagnostic characteristics of addiction/ craving and to excessive and problematic use and risk behavior link	Quality a: treatment b: diagnostic d: link (Appendix 3)
Disney et al., 2006	338	Heroin	Opioid dependent	NEP	SCID DSM-IV	Alcohol 68%, sedative 20%, THC 51%, cocaine 78% and other substances 11% dependent.	Significant association between cocaine dependence and HIV risk behavior	a) low b) low d) moderate
Hides, L. et al., 2007	103	All substances	PWID Current SUD	NEP	MINI DSM-IV	100% current substance use disorder, 25.2% current alcohol use disorder.		a) Low b) low
Gibbie et al., 2011	103	All substances	PWID Current SUD	NEP	MINI DSM-IV	100% current substance dependence, 25.2% current alcohol dependence.		a) low b) low

Note (Legend): ACASI = Audio Computer-Assisted Self-Interview; ASI = Addiction Severity Index; ASSIST = Alcohol, Smoking and Substance Involvement Screening Test; CIDI = Composite International Diagnostic Interview; HRBS = HIV Risk-Taking Behavior Scale; MINI = Mini International Neuropsychiatric Interview; N = Number of subjects; NEP = Needle Exchange program; OTI = Opiate Treatment Index; PRISM = Psychiatric Research Interview for Substance and Mental Disorders; PWID = People Who Inject Drug; RAB = Risk Assessment Battery; SCID = Structured Clinical interview for DSM; SUD = Substance Use Disorder

Table 2: Summary table of data from studies reporting craving.

Study	SUBJECTS				METHODS	RESULTS		
	N	Substance	Inclusion criteria: Diagnosis / use	Recruitment site	Craving measure and definition	craving frequency or intensity	Link between craving and excessive/problematic use or risk behavior	Quality a: treatment c: craving d: link (appendix 3)
Kipke M.D. et al., 1997	89	Illicit substances	Younger IDU in last 30 days	NEP	Ability to resist sharing needles while high or craving drugs is assessed	Craving existed	The NEP users have more confidence in their ability to resist using dirty materials when they have craving or “high” than NEP non-users.	a) Low c) Low d) Low
Kelahr, M. and Ross, M.W., 1999	84	All substances	Injection and sharing in last months	NEP	Craving defined as the degree to which the person was “hanging out” for the substance physically or psychologically.	Craving existed	The probability of sharing syringes increases with the increase of craving	a) Low c) Moderate d) Low
GU, J. et al., 2009	162	Heroin	PWID in last 6 months	NEP	“How severe is your drug craving?” 4point scale: Not at all; slight; moderate; severe	57.4% moderate /severe craving and 42.6% not at all/slight in the last month.		a) low c) Moderate

Note (Legend): N = Number of subjects; NEP = Needle Exchange program, PWID = People Who Inject Drug

Appendix 1: Search detail

DATABASE: Pubmed

Harm reduction	Supervised injection Facilities	((((((("Supervised") OR "safer")) AND (((("injection") OR "injecting") OR "shooting") OR "consumption"))) AND (((((facility) OR facilities) OR room) OR gallery) OR center) OR site)))
	Needle exchange program	Needle-Exchange Programs [MeSH Terms]
Diagnostic characteristic of Addiction	Substance use disorder diagnosis and criteria	((((((("Substance-Related Disorders/diagnosis") OR "Mental Disorders/diagnosis") OR ((drug abuse) OR drug dependence) AND diagnosis [MeSH Terms])
	craving	Motivation") OR "Drug-Seeking Behavior") OR "Craving") OR urge) OR desire) OR craving
User query	((((((((("Supervised") OR "safer")) AND (((("injection") OR "injecting") OR "shooting") OR "consumption"))) AND (((((facility) OR facilities) OR room) OR gallery) OR center) OR site))) OR "Needle-Exchange Programs"))) AND (((((((("Substance-Related Disorders/diagnosis") OR "Mental Disorders/diagnosis") OR ((drug abuse) OR drug dependence) AND diagnosis[MeSH Terms])) OR "Motivation") OR "Drug-Seeking Behavior") OR "Craving") OR urge) OR desire) OR craving)	

DATABASE: PsycINFO via EBSCOhost

S1: supervised injection sites or supervised injection facilities or safe injection sites or safe injection facilities or insite or drug consumption rooms

S2: syringe exchange programs or needle exchange programs

S3: craving

S4: substance abuse or substance use or drug abuse or drug addiction or drug use AND (diagnosis criteria OR diagnosis)

S5: (mental health or mental illness or mental disorder or psychiatric illness or psychiatric illness) AND diagnosis

User query: (S1 OR S2) AND (S3 OR S4 OR S5)

Appendix 2: PICOS criteria for inclusion of primary articles

Population:

Study population includes individuals who actively use substances outside the abstinence-oriented care context recruited in NEP and SIF.

Intervention:

-

Comparison:

-

Outcome:

Data on the prevalence of substance use disorder or abuse or dependence diagnosis or individual diagnostic criteria prevalence (DSM or ICD), or craving frequency and intensity.

Study design:

All studies.

Appendix 3: Scale for quality assessment of studies

	Severity Scale of quality		
	Low quality	Moderate quality	High quality
a) Treatment	Treatment information		No treatment information
b) Diagnostic	Diagnostic (yes/no)	Mean number of criteria endorsed	Prevalence of each diagnostic criteria
c) Craving definition	No definition	-	Explicit definition
Craving assessment	Presence (yes/no)	Level of craving (categorical measure)	Large point VAS of intensity (continue measure)
d) Link diagnostic / craving and excessive use /risk behavior	hypothetical link reported	Cross sectional association	Prospective link

Legend: MQL= Maximum quality level, VAS=Visual Analogue Scale.

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PARTIE II : les critères diagnostiques DSM-5

Manuscript 3: Item Response Theory analyses of DSM-5 substance use disorder criteria in French outpatient addiction clinic participants. How much is craving special?

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ABSTRACT

Background: To evaluate the dimensionality and psychometric validity of the 11 DSM-5 criteria for alcohol, opiates, cocaine, cannabis and tobacco use disorders, with a focus on craving, and to evaluate these properties by age, gender and psychiatric comorbidities in a French sample of subjects seeking addiction treatment.

Methods: Cross-sectional study, included participants recruited from outpatient clinics with DSM-5 substance use disorder and sought treatment for at least one addiction. Diagnostic criteria were evaluated with the Mini international Neuropsychiatric Interview. In Current regular user, defined as at least two times per week, of alcohol (n= 787), opiates (n= 131), cocaine (n= 141), tobacco (n= 1014) and cannabis (n= 504), factor and 2-parameter IRT analysis was used to investigate the dimensionality and psychometric properties of the 11 DSM-5 SUD criteria. Differential Item and Test functioning (DIF & DTF) analysis were performed across sociodemographic characteristics and psychiatric disorders.

Results: 1359 participants were included (68% male; mean age 38.7). Craving criterion had high prevalence (71% to 87%). One-factor dimensionality was confirmed, excepted for tobacco. Craving criterion had the strongest factor loadings, lower difficulty (range, -1.29 to -0.67) and higher discrimination (range, 2.11 to 3.05), and no DIF compared to other criteria. The tobacco criteria set functioned differently by mood and anxiety disorders.

Conclusions: We confirmed the unidimensionality of the 11 SUD DSM-5 criteria and indicate that craving was the most selective criterion because of its psychometric properties and had no DIF compared to other criteria, regardless of the substance in this adult clinical sample.

Keywords: DSM-5; diagnostic criteria; Substance use disorder; craving; Item response theory; Psychiatric comorbidities;

INTRODUCTION

Substances included in substance use disorders (SUD) such as alcohol, cannabis, tobacco, opioids, and cocaine induce a wide variety of adverse health consequences that are directly related to their toxic effects and as a group they are one of the most important contributors to the global burden of disease (Alcohol and Drug Use, 2018). All these substances have in common to induce in some users repeated and excessive use that characterizes SUD (Auriacombe et al., 2018). As a consequence, substance users with SUD will concentrate most negative health consequences of so-called preventable diseases. In this perspective, for an efficient reduction of the global burden of a wide variety of diseases it is paramount to reliably diagnose SUD early in time and quality diagnostic criteria are needed.

Changes were made to the SUD diagnostics in the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) to address issues with DSM-IV. Latent variable methods such as item response theory (IRT), are the preferred approach for assessing dimensional and structural validity of the diagnostic criteria (Embretson and Reise, 2000). IRT analyses allow evaluation of the psychometric properties of criteria to better understand the behavior of criteria between each other, providing information on criterion difficulty to be endorsed, corresponding on a value of the latent trait severity, and discrimination from subjects that do not have the disorder. When applied to the 11 DSM-5 SUD criteria, IRT indicate one underlying latent construct with criteria distributed across the severity continuum showing the unidimensionality of the seven dependence and three abuse criteria of DSM-IV and supported the combining of all criteria in DSM-5, and this was evident for all substances (Hasin et al., 2013; Serier et al., 2019; Shmulewitz et al., 2015). Removing legal problems was recommended because of low prevalence, low discrimination, poor fit with other criteria and little added SUD information (Hasin et al., 2013). Justifications for adding craving as a SUD criterion included the view that it is central to SUD and that it can lead to relapse (Auriacombe et al., 2018). Furthermore, studies among patients in treatment showed a prospective link between craving and substance use (Fatseas et al., 2015; Serre et al., 2015), making craving a potential proximal marker of addiction and treatment target (Auriacombe et al., 2018; Sayette, 2016). From a diagnostic perspective, several IRT analyses, showed that craving fit well with the other criteria on the underlying unidimensional latent SUD variable and its addition did not change psychometric properties for other criteria or overall model (Hasin et al., 2013; Serier et al., 2019).

Although several studies have conducted IRT analyses on the DSM-5 SUD criteria, these previous findings need to be replicated using different data sets, especially in samples of individuals who seek addiction treatment who could exhibit more symptoms and more severe symptoms of addiction than general population samples (Cherpitel et al., 2010). Available

studies in clinical samples, that include craving in the DSM-5 criteria are few and in US samples only (Hasin et al., 2013; Serier et al., 2019; Shmulewitz et al., 2015). Among studies that explored craving some differences on the severity level and discrimination properties was found (Chung et al., 2012; Hasin et al., 2012; Serier et al., 2019), but some indicated a valuable addition of craving (Chung et al., 2012). Furthermore, most available studies in clinical samples did not systematically evaluate the psychometric properties across several substances (Shmulewitz et al., 2015), and did not determine if items function differently among those with mood and anxiety disorders, which are highly comorbid with addiction (Hasin et al., 2012; Lai et al., 2015). Some diagnostic criteria of SUD could be explained by, or are very similar to the mood or anxiety disorder criteria, which are very comorbid disorders (Lai et al., 2015).

To address the current gap in knowledge of DSM-5 SUD diagnosis, we chose a French addiction treatment seeking sample, to assess prevalence of SUD with and without craving, to confirm unidimensionality and explore the psychometric properties of the criteria, to contribute to the progress of the debate on the addition of craving as a criterion and its potential special place among the other criteria. We also tested the differential item (criteria) functioning (DIF) to determine if criteria function differed by age, gender, mood or anxiety disorder, and differential test functioning (DTF) to see if such differences would affect diagnosis. Finally, we determined if the changes (combining DSM-IV criteria, adding craving) added more information about the underlying trait. The objective of the present study was to evaluate the dimensionality and psychometric validity of the 11 DSM-5 criteria for alcohol, opiates, cocaine, cannabis and tobacco use disorders, with a focus on craving, and to evaluate these properties by age, gender and psychiatric comorbidities in a French sample of subjects seeking addiction treatment.

METHODS

Sample

The sample was extracted from the Addiction Aquitaine cohort (ADDICTAQUI, Bordeaux, France) and included 1,359 participants, aged 18 years and older, who provided informed consent. Participants were recruited from outpatient clinics if they had a DSM-5 substance use disorder and sought treatment for at least one addiction. This cohort meets French Regulation requirements for clinical research, and ethics permission for the study was obtained from the French ethical research committees.

Assessments

Each subject completed a baseline interview that included a standardized and structured interview with the Mini International Neuropsychiatric interview (MINI) (Lecrubier et al.,

1997), and the Addiction Severity Index (Denis et al., 2016), administered by trained interviewers. Sociodemographic and substance use-related variables were collected with the ASI. Diagnostic criteria were evaluated with the MINI using DSM-IV for mood and anxiety disorders and DSM-IV and DSM-5 for SUD (Lecrubier et al., 1997).

Measures

Substance use and SUD diagnosis

Current regular use was defined as at least two times per week. Among regular users, the 11 DSM-5 SUD criteria were evaluated for the past 12 months. These criteria included the DSM-IV dependence and abuse criteria (except for legal problems) and an added criterion for craving (defined as “*have you experienced a strong and uncontrollable desire to use the substance?*”) (Hasin et al., 2013). DSM-5 substance use disorder (SUD) was defined according to the number of endorsed criteria: no diagnosis (0 to 1 criterion), mild (2 to 3 criteria), moderate (4 to 5 criteria) and severe (6 or more criteria) (APA, 2013; Hasin et al., 2013), using 11 criteria, as well as excluding the craving criterion.

Sociodemographic variables

Because age had a normal distribution it was dichotomized at the median (Table1).

Mood and anxiety disorders

Current mood disorder was positive if current major depressive or bipolar disorder was positive. Current anxiety disorder was positive if current generalized anxiety, panic disorder with or without agoraphobia, or social phobia were positive.

Analyses

For each substance, analyses were conducted separately among current regular users.

Sample description

Prevalence of categorical variables (gender, mood and anxiety disorders, SUD) and means of continuous variables (age, number of criteria) were calculated.

Unidimensionality

To assess the dimensionality of the 11 DSM-5 criteria, we fit a one-factor model, using confirmatory factor analysis (CFA). Unidimensionality was confirmed when the CFA model showed adequate model fit by comparative fit index (CFI) or Tucker-Lewis index (TLI) ≥ 0.95 and root mean square error of approximation (RMSEA) ≤ 0.06 (Hu and Bentler, 1999). Factor

loadings below 0.40 were considered to be only weakly related to the underlying construct (Shmulewitz et al., 2011).

Item Response Theory (IRT)

For each substance, a 2-parameter logistic IRT model was performed with the 11 DSM-5 SUD criteria, to examine each criterion difficulty (inversely related to frequency) and discrimination (how well the criterion differentiated between respondents with high and low severity of the condition). Item characteristic curves (ICC) were generated to display the estimated probability of endorsing each criterion across the underlying continuum. In the ICC, the difficulty parameter was the point on the x-axis where the probability of endorsing a criterion was 0.5 (curve toward the right indicates criteria of greater difficulty), and discrimination is the slope of the curve at that point (steeper slopes indicate greater discrimination) (Embretson and Reise, 2000; Hasin et al., 2012; Shmulewitz et al., 2011).

Differential Item Functioning (DIF)

To determine if criterion (item) functioning differed based on key patient characteristics, multiple indicator multiple cause (MIMIC) structural equation models (Woods et al., 2009), were used to model each DSM-5 criterion set as a latent variable indicated by the 11 criteria and regressed on the participant characteristics. Three models were analyzed: Model one tested for DIF by age and gender; model two tested for DIF by current mood disorder, adjusting for age and gender; and model three was similar to model two but tested for DIF by anxiety disorder. DIF was indicated when a criterion showed a statistically significant association with a participant characteristic, after accounting for the underlying association with the latent variable. This independent association (between the criterion and the characteristic) was indicated by statistically significant modification indices (MI), which suggested that adding that association to the model would improve model fit. For each participant characteristic, we tested DIF for 11 criteria, so we used Bonferroni adjustment for multiple comparisons, considering a MI significant at $p \leq 0.05/11=0.0045$.

Differential Test Functioning (DTF)

To test if the whole 11 criteria set functioned differently by participant characteristic, we calculated the average difference in the expected number of criteria for individuals with the same trait severity by participant characteristic subgroups (Raju et al., 1995; Shmulewitz et al., 2011). A difference smaller than one indicates no DTF, since that difference would lead to minimal differential SUD diagnosis by subgroup.

Due to small sample size DIF and DTF were not carried out for opiates and cocaine.

Total information

Total information curves (TIC) were generated to show their ability to discriminate individuals along the latent trait severity spectrum and total information area index (TIA) confidence intervals (CI) were calculated (bootstrap method) to indicate which criterion set provided significantly more information (Appendix).

All IRT, TIC and DIF analysis were conducted in Mplus 8 (Muthen and Muthen, 1998-2017). DTF, and TIA were conducted using Rcode (available at http://www.columbia.edu/~mmw2177/IRT/boot_irt_info.txt) (R Core Team, 2018).

RESULTS

Sample Description (Table 1 & 2)

Mean age of the sample was 39 years old, about two-third of the participants were male (67%), about one-third had current mood disorder and 42% had current anxiety disorder (*Table 1*).

The prevalence of SUD among regular users of each substance were: alcohol 92%, opiates 97%, cocaine 93%, cannabis 93% and tobacco 89%. Addition of craving as a criterion added few new cases (*Table 1*). “Craving” was among the most endorsed criterion across all substances (*Table 2–4*).

Dimensionality & IRT (Table 2–4; Figure 1)

For alcohol, opiates, cocaine and cannabis, unidimensionality was confirmed as supported by the model fit indices and factor loadings, except for “hazardous use” for opiates and cannabis (*Table 2–4*). For tobacco, unidimensionality was confirmed by RMSEA, but the TLI and CFI were slightly below the recommended 0.95 level, and factor loadings were <0.4 for “hazardous use” and “social problems”.

Across all substances, discrimination parameters ranged from 0.56 to 3.03 indicating that criteria had relatively high ability to delineate individuals who were higher vs. lower on the latent trait. In this clinical sample, the difficulty estimates of ≤ 0.0 indicated that even subjects below average on the latent trait had at least a 50% probability of experiencing the criterion.

Factor loadings for “craving” were higher than for any other diagnostic criterion (alcohol, 0.83; opiates, 0.84; cocaine, 0.90; cannabis, 0.82; and tobacco, 0.77). “Craving” criterion also

discriminated better than any other diagnostic criterion (alcohol, 2.40; opiates, 3.03; cocaine, 2.96; cannabis, 2.30; and tobacco, 2.12), and was among the least difficult criteria.

The “withdrawal” criterion had the second-highest factor loading, second-highest discrimination and low difficulty for opiates, cannabis and tobacco use disorders. “Hazardous use” had the lowest discrimination parameter for all substances.

Differential Functioning (DIF & DTF)

There was no significant DIF for the following criteria: “craving”, “using in larger amount than intended”, “time spent to use”, “activities given up because of use” and “withdrawal”. Some significant DIF was found by age and gender for alcohol, cannabis and tobacco use disorder criteria (Appendix).

For alcohol, the “difficulty to quit or control” criterion had lower difficulty in individuals without mood disorder than those with mood disorder ($p=0.003$). For tobacco, those with anxiety disorder had lower difficulty to endorse “Neglect roles” ($p<0.0001$), and those with mood disorder had lower difficulty to endorse “Having social or interpersonal problems” ($p=0.005$).

For the total criterion set (DTF), the average expected difference in number of criteria endorsed was <1 in all subgroups for alcohol (0.20 for age, 0.36 for gender, 0.24 for anxiety disorder, 0.14 for Mood disorder) and cannabis (0.69 for age, 0.26 for gender, 0.20 for anxiety disorder, 0.39 for Mood disorder). For tobacco, the average expected difference in number of criteria endorsed was <1 for gender (0.50) and age (0.28) but not for anxiety (2.68) and mood (1.01) disorder.

Total information curves (TIC) & Total Information Area index (TIA)

Addition of DSM-IV abuse and craving criteria to DSM-IV Dependence criteria increased information for some substances (Appendix).

DISCUSSION

This is the first study among a sample of French addiction-treatment-seeking subjects, to examine dimensionality, criterion difficulty and discrimination, differential item and test functioning and total information of the 11 DSM-5 SUD criteria, with a focus on craving, for five substances. In our study, unidimensionality of 11 DSM-5 criteria was confirmed, except for tobacco. Regardless of the substance, the craving criterion had higher factor loadings, one of the lower difficulty and had a higher discrimination compared to other criteria. The “craving”, “using in larger amount than intended”, “time spent to use”, “activities given up because of use” and “withdrawal” criteria functioned similarly in all subgroups for alcohol,

cannabis and tobacco. For tobacco only, the criteria set functioned differently by mood and anxiety disorder.

The prevalence of SUD was very high among current regular users. Addition of craving as a criterion added only few new cases as previously reported (Cherpitel et al., 2010; Hasin et al., 2013), suggesting that subjects with SUD before addition of the craving criterion had this criterion. The pattern of criteria endorsement was similar across substances and was high for the majority of criteria, and “Craving” was among the most endorsed criterion across all substances (Chung et al., 2012; Gilder et al., 2014; Hasin et al., 2012).

Consistent with prior studies, unidimensionality was confirmed for alcohol, opiates, cocaine and cannabis, further supporting the DSM-5 changes (Hasin et al., 2012; Hasin et al., 2013). For tobacco, some fit indices confirmed unidimensionality, while others did not (CFI and TLI), which could be due to low factor loading of two DSM-IV abuse criteria (under 0.40), suggesting their limitations as indicators of the construct (Appendix) (Shmulewitz et al., 2011). In accordance with clinical samples studies, the majority of criteria had a discrimination parameter indicating that criterion had relatively high ability to delineate individuals who were higher vs. lower on the latent trait and the majority of criteria had a low difficulty estimates, reflecting a high frequency of criteria in this sample (Appendix) (Cherpitel et al., 2010; Hasin et al., 2012; Serier et al., 2019).

Most IRT studies in clinical samples did not include or specifically explore the craving criterion parameters despite debate on this addition, and did not systematically evaluate the psychometric properties across several substances (Hasin et al., 2013; Serier et al., 2019; Shmulewitz et al., 2015). In our clinical sample of French subjects, regardless of the substance, “craving” seems the most selective criterion, because it loaded more strongly than any other diagnostic criterion, indicating that it fit well with the one-factor model, had one of the lower difficulty (more frequently endorsed) and had a higher discrimination compared to other criteria. In a study among a clinical sample of adolescents and young adults with tobacco use disorder similar results were found about “craving” that had relatively low difficulty and high discrimination in IRT analyses (Chung et al., 2012). In adult general population samples and lifetime users, studies found similar results on the discrimination power of the “craving” criterion for stimulants and alcohol use disorders (Gilder et al., 2014; Shmulewitz et al., 2011). Higher difficulty level of the “craving” criterion was found among general population and could be explained by the high power of discrimination compared to other criteria (Gilder et al., 2014; Hasin et al., 2013). In general population samples there are subjects without SUD and consistent with our results, we suggest that only those with SUD endorsed “craving” because it is very discriminant, so it is among the less endorsed among subjects without the disorder compared

to other criteria less discriminant and by consequence that may be endorsed by users without the disorder, as was found in some general sample studies (Castaldelli-Maia et al., 2015; Gilder et al., 2014; Hasin et al., 2013). These results indicated that “craving”, seems to capture the less severe end of the diagnostic spectrum and the criterion differentiated well respondents with high and low difficulty of the condition. In other words, “craving” captured well subjects with less severe SUD, which suggests, its potential usefulness as an early indicator of SUD (Chung et al., 2012). In a study with a US-clinical sample, the craving criterion loaded very highly and was among the least difficult criteria, but in contrast to our results, had an intermediate-level of discrimination compared to other criteria (Hasin et al., 2012). These differences could be attributable to the assessment tool used to evaluate the criteria (Lane et al., 2016), and notably how the craving criterion was assessed.

The “withdrawal” criterion showed the same IRT parameters specificities as craving (high factor loading, low difficulty and high discrimination), but only for opiates, cannabis and tobacco. No other IRT studies on DSM-5 criteria highlighted the highly selective characteristics of the “withdrawal” criterion as in our results. The difference across substances could be due to the differences in their pharmacology and toxic effects related to the biology of withdrawal that is consequential to use (O’Brien, 2011). For cannabis use disorder this result contributes to the relevance of the inclusion of withdrawal as a criterion in DSM-5 (Hasin et al., 2013).

Most IRT studies in clinical samples did not determine if items function differently among those with mood and anxiety disorders, which are highly comorbid with addiction (Hasin et al., 2012; Lai et al., 2015). Our DIF analyses, by age, gender, anxiety and mood disorder, indicated that “craving”, “using in larger amount than intended”, “time spent to use”, “activities given up because of use” and “withdrawal” did not work differently for alcohol, cannabis and tobacco. The majority of criteria without significant difference on difficulty level (prevalence) were criteria of the loss of control dimension of the SUD diagnosis (APA, 2013; Martin et al., 2014). Among clinical samples similar results were found for the “craving” criterion for tobacco, “time spent to use” and “activities given up because of use” criteria for cannabis (Chung et al., 2012; Hasin et al., 2012). Our DIF results are in contrast with other studies among general population and emergency department samples that showed significant difference in “craving” criterion functioning according to age, sex, ethnicity or countries for alcohol and tobacco use disorders (Castaldelli-Maia et al., 2015; Cherpitel et al., 2010; Shmulewitz et al., 2015; Shmulewitz et al., 2011). These differences may be due to greater variability in age and ethnicity in general population samples. In our study, more than half of the subjects were male and were recruited from a single substance addiction treatment site in France among French-speaking people only, which may have limited ethnicity variability. The

majority of differences of functioning on criterion difficulty were by age and gender (Appendix), but the overall alcohol, cannabis and tobacco disorder diagnosis should be unaffected because the expected number of criteria endorsed should not differ by one or more criteria for the same underlying trait severity ($DTF < 1$). Considering mood and anxiety disorders, DIF analyses indicated that the alcohol “difficulty to quit or control” criterion was more frequently endorsed by subjects without a mood disorder than subjects with a mood disorder, which may be due to fewer attempts to stop (or reduce) use in subjects with mood disorders because they used alcohol as self-medication. (Turner et al., 2018) For Tobacco “social/interpersonal problem due to use” and “neglect roles because of use” criteria were more frequent among subjects with anxiety or mood disorders, inducing a difference in the average expected number of criteria endorsed, suggesting that these criteria may not work well in anxiety or mood subgroups, (Hasin et al., 2013) and can indicate a poorly functioning criterion for sensitivity (Shmulewitz et al., 2015).

In accordance with other studies, the few additional cases identified for the 5 substances and the no significant increase of total information when craving was added for the majority of substances (Appendix), suggested that it is largely redundant with other criteria (Cherpitel et al., 2010; Hasin et al., 2013).

Study limitations are acknowledged. As with many substance use studies, information is vulnerable to self-report bias. However, since self-reported substance use tends to be accurate in the absence of sanctions (Magura et al., 1987), and since the subjects reported a high prevalence of the SUD criteria, we doubt that self-report bias influenced the results significantly. Furthermore we previously reported that self-report use data was reliable when compared with toxicology analysis (Denis et al., 2012). Also, we used a measure (MINI) with good test-retest reliability that is well validated and used in numerous studies in the world. In addition, all subjects were included in the same clinical setting. Studies with greater geographic distribution, including different countries across Europe with cultural diversities, would be important in future studies.

In conclusion, we confirmed in a sample of French addiction treatment-seeking adults the dimensional and structural validity of the 11 DSM-5 criteria on a latent construct, measuring use disorder, previously reported in US clinical samples. Furthermore, in the debate on the addition of craving for the improvement of SUD diagnosis this study highlights that the “craving” criterion is the most selective criterion for the 5 substances in this sample. It has the same behavior regardless the type of substance compared to other criteria, and could be

considered as a strong criterion of the loss of control dimension of SUD. Results suggested that “craving” and the other criteria were redundant. Whether “craving” could be sufficient to diagnose the loss of control dimension of SUD that is core to this disorder remains to be explored (Auriacombe et al., 2018; Martin et al., 2014).S Building on this research in outpatient addiction clinic participants, performance of the craving criterion should be re-examined in non-treatment settings to inform on the applicability of this criterion as a potential early and specific criterion in general population samples.

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Authors' contributions

Marc Auriacombe was the overall principal investigator of the study, obtained funding and access to participants. Deborah Hasin and Dvora Shmulewitz supervised IRT analysis. Charlotte Kervran, Fuschia Serre and Marc Auriacombe developed the study design and methods. Charlotte Kervran, Fuschia Serre, participated in patient recruitment and data collection. Charlotte Kervran, Dvora Shmulewitz, Marc Auriacombe, Deborah Hasin and Malki Stohl undertook analysis and interpretation of data and drafting of manuscript. Marc Auriacombe, Deborah Hasin, Charlotte Kervran, Dvora Shmulewitz, Fuschia Serre and Cécile Denis undertook the critical revision of the manuscript for important intellectual content. All authors significantly contributed to the manuscript and approved the final version.

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Table 1: Demographic, substance-use related variables, DSM-5 diagnostic severity and endorsed criteria in an outpatient addiction clinic sample by substance user groups

	Total sample	Alcohol (n=787)	Opiates (n=131)	Cocaine (n=141)	Cannabis (n=504)	Tobacco (n=1014)
Age – Mean (SD)	38.6 (11.5)	40.3 (11.6)	34.3 (9.7)	32.8 (7.8)	33.5 (9.6)	38.3 (11.3)
Age – Median		39	33	32	32	37
Males – n (%)	914 (67.3)	569 (72.3)	89 (67.9)	115 (81.6)	398 (79.0)	660 (65.1)
Mood Disorder – n (%)	420 (31.1)	548 (70.1)	83 (64.3)	103(73.1)	172 (34.3)	683 (67.6)
Anxiety Disorder – n (%)	561 (41.5)	475 (60.7)	66 (51.6)	83 (58.9)	237 (47.4)	590 (58.6)
DSM-5 criteria						
No. endorsed SUD criteria – Mean (SD)	-	6.88 (3.0)	7.37 (2.6)	7.2 (3.2)	6.69 (2.9)	5.04 (2.3)
SUD without craving – n (%)		725 (92.1)	127 (96.9)	131 (92.9)	466 (92.5)	904 (89.2)
No diagnosis		62 (7.8)	4 (3.1)	10 (7.1)	38 (7.5)	110 (10.8)
Mild		75 (9.5)	9 (6.9)	19 (13.5)	64 (12.7)	262 (25.8)
Moderate		158 (20.1)	33 (25.2)	20 (14.2)	101 (20.0)	348 (34.3)
Severe		492 (62.5)	85 (64.9)	92 (65.3)	301 (59.6)	294 (29.0)
SUD with craving – n (%)		728 (92.5)	128 (97.7)	133 (94.3)	474 (94.1)	928 (91.5)
No diagnosis		59 (7.5)	3 (2.3)	8 (5.7)	30 (5.9)	86 (8.5)
Mild		60 (7.6)	7 (5.3)	17 (12.1)	56 (11.1)	157 (15.5)
Moderate		122 (15.5)	23 (17.6)	15 (10.6)	78 (15.4)	334 (32.9)
Severe		546 (69.4)	98 (74.8)	101 (71.6)	340 (67.5)	437 (43.1)

SD: standard deviation, SUD: Substance use disorder

Table 2: Parameter estimates from Confirmatory factor analysis/item response theory analysis: Alcohol and Opiates.

	Alcohol (n=787)				Opiates (n= 131)			
	Factor loading	Prevalence (%)	IRT parameters		Factor loading	Prevalence (%)	IRT parameters	
			(b) Difficulty (S.E)	(a) Discrimination (S.E)			(b) Difficulty (S.E)	(a) Discrimination (S.E)
Tolerance	0.627	65.3	- 0.61 (0.09)	1.35 (0.14)	0.614	84.7	-1.61 (0.41)	1.41 (0.50)
Withdrawal	0.737	49.3	0.04 (0.06)	2.00 (0.20)	0.811	90.1	-1.46 (0.23)	2.96 (0.92)
Large amount/longer	0.496	82.5	-1.88 (0.23)	0.97 (0.14)	0.782	73.3	-0.78 (0.16)	2.36 (0.61)
Quit/control	0.718	66.6	-0.58 (0.07)	1.73 (0.18)	0.664	83.2	-1.39 (0.29)	1.63 (0.51)
Time spent	0.649	52.0	-0.06 (0.07)	1.47 (0.15)	0.660	61.8	-0.47 (0.18)	1.48 (0.41)
Activities given up	0.781	52.1	-0.05 (0.06)	2.36 (0.24)	0.719	60.3	-0.37 (0.15)	1.89 (0.46)
Psychological/physical problems	0.667	59.1	-0.33 (0.07)	1.53 (0.15)	0.510	64.9	-0.73 (0.26)	1.03 (0.30)
Neglect roles	0.616	52.0	-0.07 (0.07)	1.31 (0.14)	0.741	29.8	0.74 (0.20)	1.72 (0.46)
Hazardous use	0.414	73.4	-1.54 (0.22)	0.73 (0.11)	0.361	52.7	-0.18 (0.30)	0.65 (0.25)
Social/interpersonal problems	0.729	65.1	-0.51 (0.07)	1.80 (0.18)	0.648	50.4	-0.03 (0.17)	1.48 (0.36)
Craving	0.829	71.2	-0.66 (0.07)	2.40 (0.26)	0.843	86.3	-1.24 (0.21)	3.03 (1.10)
Model fit indices								
CFI	0.963				0.963			
TLI	0.954				0.954			
RMSEA	0.057				0.057			

S.E.: Standard Error, CFI: Comparative Fit Index, TLI: Tucker Lewis Index, RMSEA: Root Mean Square error of approximation

Table 3: Parameter estimates from Confirmatory factor analysis/item response theory analysis: Cocaine and Cannabis.

	Cocaine (n=141)				Cannabis (n=504)			
	Factor loading	Prevalence (%)	IRT parameters		Factor loading	Prevalence (%)	IRT parameters	
			(b) Difficulty (S.E)	(a) Discrimination (S.E)			(b) Difficulty (S.E)	(a) Discrimination (S.E)
Tolerance	0.763	68.8	-0.65 (0.17)	1.84 (0.44)	0.631	66.7	-0.68 (0.11)	1.35 (0.19)
Withdrawal	0.682	58.9	-0.32 (0.17)	1.49 (0.36)	0.765	69.0	-0.66 (0.09)	1.89 (0.28)
Large amount/longer	0.685	78.0	-1.16 (0.25)	1.51 (0.36)	0.667	60.1	-0.38 (0.09)	1.49 (0.20)
Quit/control	0.685	62.4	-0.46 (0.18)	1.49 (0.36)	0.650	60.3	-0.40 (0.09)	1.43 (0.19)
Time spent	0.804	68.1	-0.57 (0.16)	2.23 (0.52)	0.648	55.4	-0.20 (0.09)	1.42 (0.19)
Activities given up	0.852	58.2	-0.20 (0.13)	2.85 (0.68)	0.647	55.4	-0.20 (0.09)	1.44 (0.19)
Psychological/physical problems	0.781	63.1	-0.42 (0.15)	1.98 (0.46)	0.593	56.7	-0.28 (0.10)	1.24 (0.17)
Neglect roles	0.695	46.1	0.17 (0.15)	1.60 (0.40)	0.499	39.3	0.55 (0.13)	0.96 (0.16)
Hazardous use	0.434	74.5	-1.61 (0.54)	0.74 (0.26)	0.326	70.6	-1.67 (0.38)	0.56 (0.13)
Social/interpersonal problems	0.607	66.0	-0.69 (0.22)	1.21 (0.31)	0.584	56.5	-0.28 (0.10)	1.17 (0.17)
Craving	0.900	78.0	-0.88 (0.16)	2.96 (0.86)	0.817	79.0	-1.00 (0.10)	2.30 (0.34)
Model fit indices								
CFI	0.995				0.967			
TLI	0.993				0.958			
RMSEA	0.026				0.048			

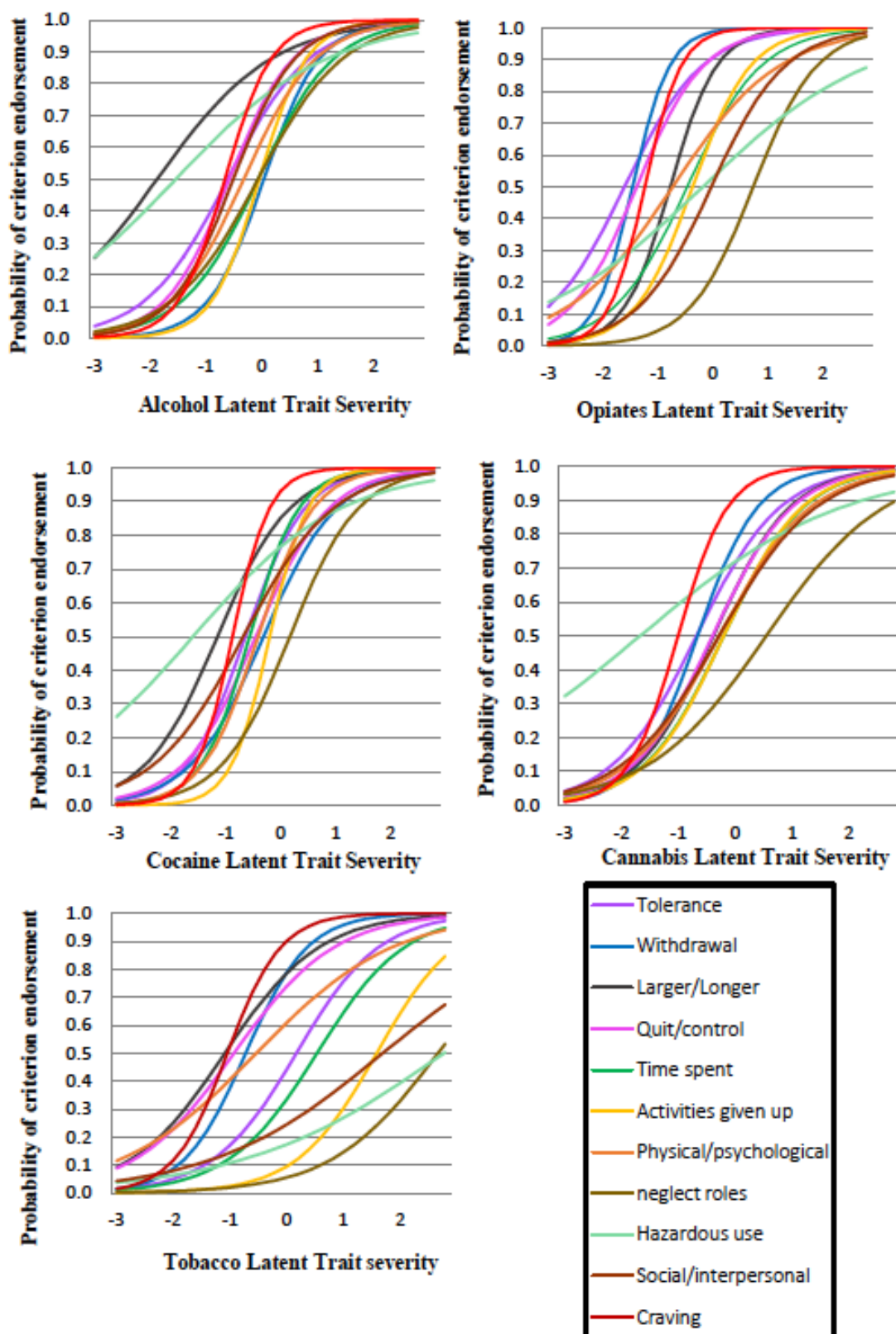
S.E.: Standard Error, CFI: Comparative Fit Index, TLI: Tucker Lewis Index, RMSEA: Root Mean Square error of approximation

Table 4: Parameter estimates from Confirmatory factor analysis/item response theory analysis: Tobacco.

Tobacco (n=1014)				
	Factor loading	Prevalence (%)	IRT parameters	
			<i>(b)</i> Difficulty (S.E)	<i>(a)</i> Discrimination (S.E)
Tolerance	0.627	45.8	0.17 (0.06)	1.36 (0.14)
Withdrawal	0.723	70.1	-0.72 (0.07)	1.83 (0.20)
Large amount/longer	0.582	73.6	-1.09 (0.11)	1.20 (0.13)
Quit/control	0.550	69.7	-0.92 (0.10)	1.13 (0.13)
Time spent	0.598	37.3	0.54 (0.08)	1.28 (0.14)
Activities given up	0.596	15.6	1.59 (0.15)	1.41 (0.19)
Psychological/physical problems	0.463	59.5	-0.53 (0.10)	0.83 (0.10)
Neglect roles	0.476	8.30	2.68 (0.36)	1.06 (0.19)
Hazardous use	0.312	18.7	2.78 (0.48)	0.56 (0.10)
Social/interpersonal problems	0.389	26.3	1.70 (0.26)	0.66 (0.10)
Craving	0.769	79.1	-1.04 (0.08)	2.12 (0.25)
Model fit indices				
CFI	0.930			
TLI	0.912			
RMSEA	0.052			

S.E.: Standard Error, CFI: Comparative Fit Index, TLI: Tucker Lewis Index, RMSEA: Root Mean Square error of approximation

Figure 1: Item characteristic curves models of alcohol, opiates, cocaine, cannabis and tobacco DSM-5 use disorder



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Appendix

Item Response Theory analyses of DSM-5 substance use disorder criteria in French outpatient addiction clinic participants. How much is craving special?

Statistical analysis

Total information

Total information curves (TIC) were generated for each criterion set to show their ability to discriminate individuals along the latent trait severity spectrum. A “flat” TIC indicates equal information across all severities; a “peaked” TIC indicates more information about the trait at a specific severity. We compared four curves from four sets: all 11 DSM-5 criteria; DSM-5 criteria excluding craving (10 criteria); all 7 DSM-IV dependence criteria; and DSM-IV dependence criteria including craving (8 criteria). A summary of the overall total information provided by each criterion set was indicated by the total information area index (TIA) (De Ayala, 2009). TIA confidence intervals (CI) were calculated using the bootstrap method (R Core Team, 2018; Shmulewitz et al., 2011). The 2.5 and 97.5 percentiles of the TIA bootstrap distribution indicated the 95% confidence interval (CI) for TIA. Non-overlapping 95% CIs for the TIAs indicated which criterion set provided significantly more information.

Results

Differential Item functioning by age and gender

Age

For cannabis, the “hazardous use” criterion was less difficult ($p < 0.01$) (i.e. endorsement more likely at the same latent trait level) in older subjects than younger subjects. For alcohol, “tolerance” and “neglect roles because of use” criteria were less difficult in younger subjects than older ($p < 0.0001$ and $p < 0.01$ respectively) and “physical/psychological problems” criterion was less difficult in older subjects than younger ($p < 0.01$). For tobacco, “difficulty to quit or control” was less difficult in older than younger subjects ($p < 0.0001$).

Gender

For alcohol and tobacco, the “hazardous use” criterion had lower difficulty in males than females (p 's < 0.0001).

Total information curves (TIC) & Total Information Area index (TIA) (Table S1)

TIC showed an increased information across the severity spectrum as additional criteria were included for the 5 substances, but reflected little change in ability of the model to capture a greater or different range of severity of the underlying continuum of disorder (*Figure S1*). For alcohol, TIA (95% CI) showed that the addition of abuse items and abuse plus craving to the

DSM-IV dependence items significantly increased the total information (*Table S1*). For cannabis, the addition of the abuse items and craving added information above the DSM-IV dependence criteria. For tobacco, the addition of craving significantly increased the total information when added to the dependence criteria or to the 10 dependence plus abuse criteria; the addition of the abuse items also added information (*Table S1*).

Figure S1: Total information curves for DSM-5 alcohol, opiates, cocaine, cannabis and tobacco among current users of substances.

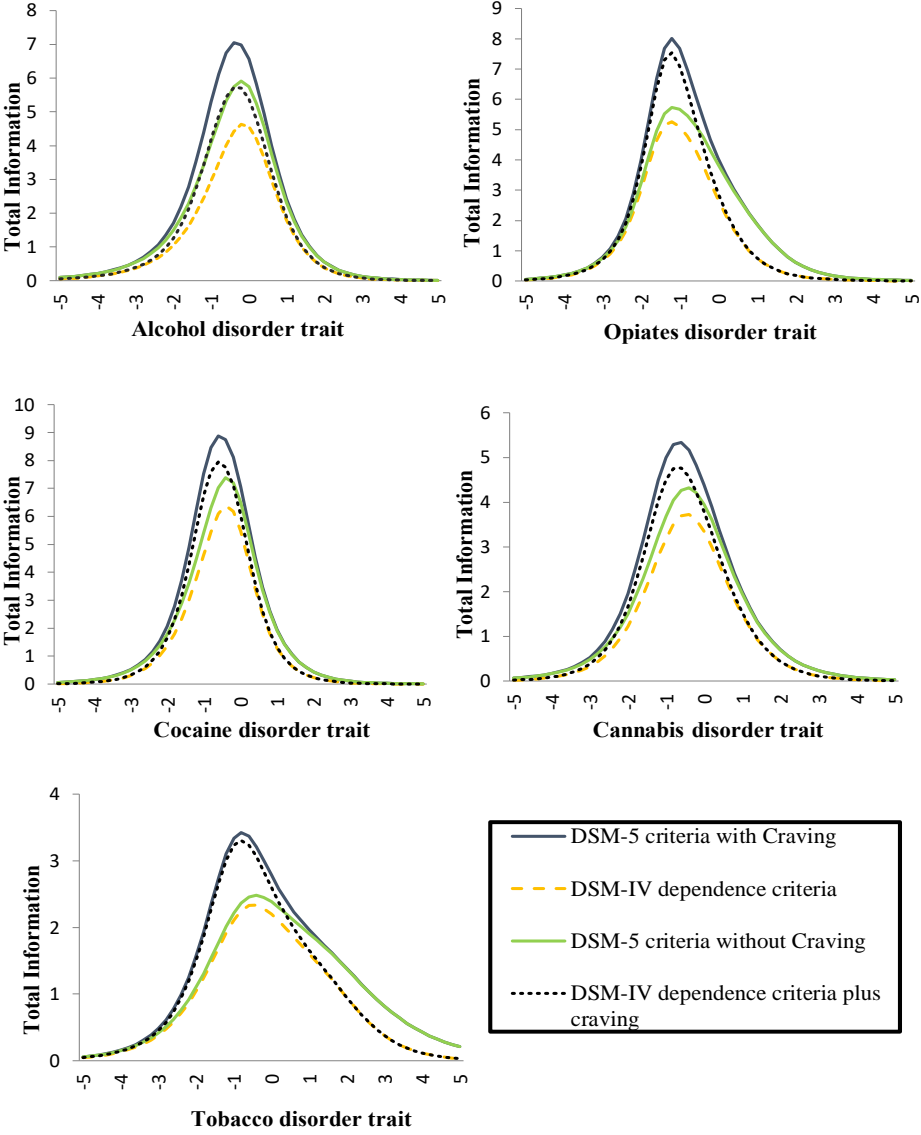


Table S1: Total information area (TIA) and 95% confidence intervals for different criteria sets.

Total Information Area index (95% CI)				
	DSM-IV Dependence (7 criteria)	DSM-IV Dependence plus Craving (8 criteria)	DSM- 5 without Craving (10 criteria)	DSM- 5 with Craving (11 criteria)
Alcohol	11.3 (10.3, 12.8)	13.98 (12.8, 15.5)	15.24_a (14.0, 17.0)	17.68_{a,b} (16.2, 19.5)
Opiates	12.59 (10.1, 31.7)	16.18 (13.2, 48.2)	16.46 (13.7, 33.5)	19.72 (16.7, 50.5)
Cocaine	14.26 (11.7, 29.2)	17.03 (15.3, 34.4)	17.20 (14.6, 24.1)	20.01 (17.1, 35.2)
Cannabis	10.27 (9.0, 11.7)	12.80 (11.4, 14.7)	12.88 (11.6, 24.1)	15.23_a (13.6, 17.2)
Tobacco	9.15 (8.4, 10.0)	11.26_a (10.4, 12.3)	11.29_a (10.4, 12.4)	13.43_{a,b,c} (12.5, 14.7)

a= Bold indicates TIA is significantly different (p-value<0.5) from the DSM-IV dependence criteria set TIA. Significance is determined by non-overlapping 95% confidence intervals.

b= Bold indicates TIA is significantly different (p-value<0.5) from the DSM_IV dependence plus Craving criteria set TIA. Significance is determined by non-overlapping 95% confidence intervals.

c= Bold indicates TIA is significantly different (p-value<0.5) from the DSM-5 without Craving criteria set TIA. Significance is determined by non-overlapping 95% confidence intervals.

Discussion

Unidimensionality of Tobacco

For tobacco, some fit indices confirmed unidimensionality, while others did not (CFI and TLI). Interestingly, the factor loading of “social/interpersonal problem due to use” and “hazardous use” were under 0.40 for tobacco use disorder, suggesting their limitations as indicators of the construct (Shmulewitz et al., 2011). Another study including the abuse tobacco use disorder criteria in a clinical sample found, as our results, that tobacco abuse criteria showed relatively low frequency, low factors loading, poor discrimination and were in the high range of difficulty (Chung et al., 2012). These results contrast with a study from an Israeli sample that showed that interpersonal problems and Hazardous use criteria did fit well with the other tobacco items (Shmulewitz et al., 2011). The applicability of the DSM IV abuse criteria to Tobacco was controversial (Hughes, 2006). Whether this means that there are two separate but related disorders or that some criteria items are not particularly relevant to tobacco, as for DSM-IV “legal problems due to use”(Hasin et al., 2013), will need to be investigated in future studies.

IRT general interpretation

Across all substances, the majority of criteria had a discrimination parameter indicating that criterion had relatively high ability to delineate individuals who were higher vs. lower on the latent trait. In accordance with other clinical samples, the majority of criteria had a difficulty estimates under zero indicating that even subjects below average on the latent trait had at least a 50% probability of experiencing the criterion, reflecting a high frequency of criteria in this

sample observable by clustering the ICC curves to the left of the difficulty latent trait (Cherpitel et al., 2010; Hasin et al., 2012; Serier et al., 2019).

Similar to the “legal problem” criteria of DSM-IV (Hasin et al., 2013), “hazardous use” for tobacco and opiates in our study added poor information because it was rare and had poor discrimination as reported in previous studies (Chung et al., 2012; Hasin et al., 2012; Shmulewitz et al., 2011). In contrast for alcohol, cocaine and cannabis, the “hazardous use” criterion, was in the low range of difficulty (frequently endorsed), but still showed poor discrimination as for tobacco and opiates. The effect of including a criterion with poor discrimination suggests a risk for false positive endorsements, especially at the lower range of difficulty (high frequency) in the diagnosis that could increase “error” (Chung et al., 2012). In addition, “hazardous use” showed the most different functioning across covariates and substances, suggesting potential limitations in the performance of this criterion.

Differential item Functioning by age and gender

The majority of differences of functioning on criterion difficulty were by age, probably due to the total duration of lifetime use, and gender. It seems of interest to use the duration of use or the age of SUD start as a covariate in future studies. Males had more frequently endorsed (lower difficulty) the “hazardous use” criterion than females for tobacco and alcohol use disorders suggesting that these criteria may not work well in female subgroups (Derringer et al., 2013). As shown in a study, males were significantly higher than females on all of the sensation seekers scale scores (Shulman et al., 2015; Zuckerman et al., 1978), explaining that males reported more situations physically at risk under the influence of alcohol, considering in addition the disinhibition induced by alcohol use. This will need to be monitored in future studies.

Total information curves (TIC) & Total Information Area index (TIA)

The TIC and TIA in this French clinical sample showed an increased information of SUD as additional criteria were included for the 5 substances, but reflected little change in ability of the model to capture a greater or different range of severity of SUD disorder. Our results showed that the addition of craving alone to the DSM-IV dependence criteria significantly increased the total information for alcohol and tobacco, and only for tobacco, the addition of craving increased significantly the total information from the 10 other DSM-5 criteria set.

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Manuscript 4: Comparison of substance users seeking treatment and substance users in harm reduction settings on DSM-5 Substance Use Disorder diagnosis

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ABSTRACT

Introduction: The aim of this study was to compare substance users (SU) in harm reduction settings (HR) and SU seeking treatment for addiction (Tx) on substance use disorder (SUD) diagnostic characteristics, and craving frequency and intensity in past 30 days for five substances.

Methods: SU who sought Tx (n=1,143) and SU in HR settings (n=130) in Bordeaux, France were assessed with the Addiction Severity Index, a visual numerical craving scale and DSM-5 SUD criteria. Pearson's chi-squared test was performed for categorical variables and student-t test or a Welch test for continuous variables for univariate analysis and logistic and linear regression models were used to adjusted diagnostic characteristics, and craving comparison on sociodemographic and other addiction variables. Benjamini-Hochberg procedure was used to control the false discovery rate.

Results: Analyses were conducted separately for current users (used the substance at least 2 times per week for 12 months) of alcohol (Tx n= 787, HR n=89), opiates users (Tx n= 131, HR n=102), cocaine users (Tx n= 141, HR n=82), cannabis users (Tx n= 504, HR n=95) and tobacco users (Tx n= 1014, HR n=128). HR subjects were younger than Tx (test value, $p<.0001$). There was no significant difference in the prevalence of SUD diagnosis, but the prevalence of diagnostic criteria studied individually was slightly different between HR and Tx. Although the craving diagnostic criterion prevalence was similar in both subgroups and for the 5 substances, craving frequency, but not intensity was significantly lower for cannabis, tobacco and opiates in HR subjects.

Conclusion: SU in harm reduction settings have as much SUD diagnosis than SU seeking addiction treatment, but the criteria distributions were different according to the care settings. Substance users in harm reduction settings seem to have fewer craving episodes but at equal intensity than subjects seeking addiction treatment.

Keywords: Substance use disorder, Severity of addiction, Craving, Harm Reduction participants, patient seeking treatment.

INTRODUCTION

Harm reduction (HR) interventions aim to reduce the harm that substances cause to individuals without aiming at reducing substance use (Des Jarlais 1995, Marlatt 1996, Little, Hodari et al. 2008, Little, Franskoviak et al. 2013, Hawk, Coulter et al. 2017, Association Accessed 5 Aug 2019). Among HR settings, Needle Exchange Programs (NEP) adopted in many countries to face the HIV epidemic among people who inject drugs (PWID), were the first form of HR program (Gibson, Flynn et al. 2001, Moatti, Vlahov et al. 2001, Fatseas, Denis et al. 2012, Degenhardt, Peacock et al. 2017). Participants of these programs are well documented as a group with excessive and problematic use, many risk-practices and vulnerabilities (Moracchini, Frauger et al. 2012, Potier, Laprevote et al. 2014), but how the substance use disorder (SUD) criteria are applicable to this substance using population is unknown (Kervran, Serre et al. 2018).

Few studies examined SUD diagnostic criteria among NEP participants (Kervran, Serre et al. 2018). While, the prevalence of SUD seems similar across studies (Brienza, Stein et al. 2000, Kidorf, Disney et al. 2004, Kidorf, Disney et al. 2005, Disney, Kidorf et al. 2006, Hides, Lubman et al. 2007, Gibbie, Hides et al. 2011, Kervran, Serre et al. 2018), none of them informed on the prevalence and distribution of each individual diagnostic criterion. One study indicated a high number of lifetime SUD and current SUD in addition to opioid dependence (Kidorf, Disney et al. 2004), highlighting that poly-addiction was common.

SUD is characterized by loss of control of use, relapse, and craving (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018). Many studies have shown a predictive link between craving as a dynamic phenomenon that can change quickly during the same day, and substance use (Tiffany et Wray 2012, Moore, Seavey et al. 2014, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Sayette 2016). While previous research reported that craving was one of the most reported reasons for taking risks in sharing injection equipment (Perngmark, Vanichseni et al. 2008) and some studies discuss the implication of craving in at-risk practices (Kipke, Unger et al. 1997, Kelaher et Ross 1999), only one study assessed the level of craving among NEP participants and showed that moderate to severe substance craving was reported by more than half of participants (Gu, Wang et al. 2009).

A French study comparing substance users in addiction treatment to substance users in harm reduction settings, showed that HR participants were more precarious, younger and injected more (Moracchini, Frauger et al. 2012), but no information was available about potential differences on SUD characteristics between these two populations. While each SUD criteria were well documented among substances users seeking reduced use or abstinence treatment (Hasin, Fenton et al. 2012, Kervran, Shmulewitz et al. 2019, Serier, Venner et al.

2019), there is an important lack of data among substances users seeking help to reduce negative consequences of use without changing use in HR settings, a substance-use-friendly environment. The aim of this study was to compare substance users in harm reduction settings (HR) and substance users seeking treatment (Tx) on substance use disorder diagnostic characteristics, and craving frequency and intensity in past 30 days for five substances.

METHODS

Participants

Participants were selected from the Bordeaux site of two prospective cohort studies, Addiction Aquitaine cohort (ADDICTAQUI) and COhort to identify Structural and INdividual factors associated with drug USe (COSINUS). The inclusion criteria were: over 18 years old, French-speaking and documented informed consent. To avoid duplicate enrollment, the month, year and place of birth were collected. Both cohorts meet French Regulation requirements for clinical research (CNIL, CPP, CEEI/IRB) (Auriacombe, Roux et al. 2019, Auriacombe Accessed september 2019). Participants from ADDICTAQUI cohort were substance users seeking treatment (Tx) for at least one addiction recruited at their entry in treatment (Auriacombe Accessed september 2019). All new participants meeting DSM-5 use disorder for their main addiction were offered to participate. Participants from COSINUS cohort were substance users in harm reduction settings (HR) recruited if they reported injecting illegal substances (heroin, cocaine / crack, amphetamines, ecstasy except cannabis), or medications (methylphenidate, buprenorphine, benzodiazepines, morphine sulfate, oxycodone, methadone) at least once during the past month (Auriacombe, Roux et al. 2019).

Procedure

All assessments were performed by trained clinical research evaluators who had no involvement in treatment or HR intervention. The Addiction Severity Index, Mini International Neuropsychiatric Interview and visual numerical craving scale, assessed the two samples.

Instruments

The Mini International Neuropsychiatric Diagnostic interview (MINI) is a highly reliable and valid structured diagnostic interview providing standardized assessment of psychiatric diagnosis defined according to axis I of DSM-IV (Sheehan, Lecrubier et al. 1998). The MINI was administered by interviewers who received extensive structured training and supervision. For the purpose of the study, the 11 criteria of DSM-5 SUD were assessed (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013).

The Addiction Severity Index (ASI) is a semi-structured interview for use among problem substance users (McLellan, Kushner et al. 1992). We used a modified and validated French version of the ASI to take into account tobacco and behavioral addictions (Denis, Fatseas et al. 2016). The ASI explores seven areas of the subject's life that may be affected by the use of addictive substances or behaviors: medical status, employment/support status, substances (including alcohol, tobacco, behaviors, gambling, eating disorders), family and social relationships, legal status and psychological status.

The visual numerical craving scale is a self-reported assessment of craving frequency and craving intensity over the past 30 days rated from 0 (no craving) to 10 (extreme craving).

Measures

Sociodemographic variables

For analysis, level of education was dichotomized as less than 12 years vs. 12 years of education or more. Current work was recoded as at least 1 day versus no days working in past 30 days.

Substance use

For each substance (alcohol, opiates, cocaine, cannabis and tobacco), regular use was defined as at least 2 times per week for 12 months. The number of days of use over the past 30 days was recoded into: at least 1 day of use vs. no use in past 30 days. Current opioid agonist treatment (OAT) (methadone, buprenorphine) was recoded as at least one treatment prescribed in past 30 days.

Craving

Among regular users, for each substance, the frequency of craving in past 30 days differentiated participants with daily craving episodes from those with less than 30 days of craving. Frequency, mean and maximum intensity of craving was described among those reporting at least 1 days of craving in past 30 days.

Substance use disorder

Among regular users, for each substance, each of the 11 DSM-5 SUD criteria was evaluated for the past 12 months. More than one SUD among alcohol, opiates, cocaine, cannabis and tobacco qualified for poly-addiction.

For each substance, DSM-5 SUD severity was defined according to the number of endorsed criteria i.e., no diagnosis (0 to 1 criterion), mild (2 to 3 criteria), moderate (4 to 5 criteria) and severe (6 or more criteria) (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013).

Statistical Analysis

For the present study, current (past 12 months) regular users of at least one substance among alcohol, cocaine, tobacco, opiates and cannabis were extracted from the cohorts: 1359 participants from the ADDICTAQUI (Tx) cohort and 130 participants from the COSINUS (HR) cohort. The current regular users of each substance were compared between the two samples, e.i. current alcohol regular users of HR subgroup were compared to current alcohol regular users of Tx subgroup.

Sample description

Prevalence of categorical variables and means of continuous variables were calculated.

Univariate analysis

For univariate analysis, categorical variables were compared using Pearson's chi-squared test (χ^2) or a non-parametric exact Fisher test and continuous variables were compared using non-parametric Wilcoxon test or a Welch test, accounting for the differences of the number of participants between the two samples when the variance was unequal. For SUD criteria, a logistic regression model was performed to explore the prevalence differences of criteria between HR and Tx subgroup adjusted on age, gender, level of education, poly-addiction and number of current substance use years.

For craving characteristics in past 30 days, a logistic or linear regression model, depending if it was categorical or continuous variable, was performed to explore the differences of craving variables in past 30 days between HR and Tx subgroup adjusted on age, gender, level of education, poly-addiction and number of days of substance use in past 30 days.

The false discovery rate (FDR) is the ratio of the number of false positive results to the number of total positive test results. The FDR approach adjusts the p-value for a series of tests. We used the Benjamini-Hochberg procedure (Benjamini et Hochberg 1995) to control the FDR.

RESULTS

Total sample (Table 1)

The majority of participants were males. HR participants were significantly younger, less educated and more jobless. Ninety-nine percent of HR participants qualified for poly-addiction and had significantly higher number of SUD diagnoses. Thirty percent of HR participants reported no substance use as the main problem.

Current alcohol users (Tx n= 787, HR n=89)

HR participants used alcohol significantly more days in past 30 days, but were significantly less likely to report alcohol use as the main problem. HR participants endorsed significantly less the “large amount/longer” ($p=.0001$), and “hazardous use” ($p=.008$) criteria. No significant difference of frequency and intensity of craving in past 30 days was found.

Current opiate users (Tx n= 131, HR n=102)

HR participants were significantly more to use several opiates, and used methadone significantly more days in past 30 days. The means number of years of regular use of heroin and methadone were significantly higher among HR participants compared to Tx participants. HR participants were significantly less likely to report opiate use as the main problem. No significant difference for prevalence of opiate use disorder criteria in past 12 months was found. HR participants were less likely to report daily craving for opiates, but at the same intensity in the past 30 days.

Current cocaine users (Tx n= 141, HR n=82)

HR participants used cocaine significantly more days in past 30 days and more years during lifetime compared to Tx participants. The only significant difference between the two samples was the prevalence of the “withdrawal” criterion ($p=.0001$) that was less frequent among HR participants.

Current cannabis users (Tx n= 504, HR n=95).

HR participants used cannabis significantly more days in past 30 days and more years lifetime, but were significantly less likely to report cannabis use as the main problem. HR participants endorsed significantly less “withdrawal” ($p<.0001$), “large amount/longer” ($p=.006$), “quit/control” ($p<.0001$) and “physical/psychological problem” ($p=.008$) criteria. In past 30 days HR participants were less likely to report cannabis craving ($p<.0001$). HR participants were less to report daily cannabis craving episode and among those reporting craving in past 30 days, HR participants reported less days of craving.

Current tobacco users (Tx n= 1014, HR n=128)

HR participants used tobacco significantly more days in past 30 days, but were significantly less likely to report tobacco use as the main problem. HR participants had significant lower prevalence for the “quit/control” ($p<.0001$), and significant higher prevalence for “time spent” ($p=.001$), “neglect roles” ($p<.0001$), “hazardous use” ($p<.0001$) criteria. Among those reporting craving for tobacco in past 30 days, HR participants reported less days of craving.

DISCUSSION

To address the lack of data among substance users in harm reduction settings (Kervran, Serre et al. 2018), and test the applicability of SUD diagnostic criteria and craving as a dimensional phenomenon, this study compared SUD criteria prevalence and craving frequency and intensity between substance users in HR settings and substance users seeking treatment. Considering SUD characteristics, while there was no difference between HR and Tx subgroups on the prevalence of SUD diagnosis, there were significant differences on the prevalence of some of the individual diagnostic criteria endorsed. The “craving” criterion was the only loss of control criterion without prevalence differences between the two samples and across the 5 substances. For craving as a dimension, HR participants reported fewer episodes of craving than Tx participants but at equal intensity when reported.

The lower level of education, mean age and current working activity of substance users in HR settings was consistent to other studies with similar populations (Moracchini, Frauger et al. 2012). Among current regular users of each substance, substance users in HR settings used significantly more in the past 30 days and lifetime (Ross, Teesson et al. 2005, Moracchini, Frauger et al. 2012), but were significantly less likely to report this current regular substance use as a main problem, except for cocaine. Interestingly, 30 % of HR participants did not report substance use as a problem. This could be due to low insight, or because other problems overshadowed substance use (e.i. socio-economic condition), or because substance use was motivated by self-medication for other psychiatric disorders. People could have different conceptions of how they want to live, and, within some sociocultural contexts, some may consider their use as a simple habit. Furthermore, if substances are readily available, having a life revolving around these substances may not be experienced as a problem (Pickard et Ahmed 2016). Almost all substances users in HR settings subjects included in each subgroup of substances have a poly-addiction (Kidorf, Disney et al. 2004), unlike the substance users seeking treatment. However, the majority of subjects seeking treatment also have polyaddiction, but have a significantly lower average number of polyaddiction. Opiate users in HR settings were significantly more to use multiple opiates, methadone, and other opiates as morphine, but there was no difference on use of prescribed methadone suggesting more non-prescribed methadone use, warning on the risks of overdose in this HR population (Reimer, Wright et al. 2016).

While there was no difference between substance users in harm reduction settings and substance users seeking treatment on the prevalence of SUD diagnosis regardless of substances used, there were some significant differences on prevalence of each individual diagnostic criterion. Harm reduction participants had lower prevalence for most criteria. Some loss of control criteria, “difficulty to quit or control” and “use in large amount or longer than intended” were less frequently endorsed by alcohol, cannabis and tobacco current users, in harm reduction settings. Substance users in harm reduction settings could be either more interested in reducing harm than controlling alcohol, cannabis or tobacco use, less a main problem (Pickard et Ahmed 2016), than users seeking treatment, or they could have been more successful in controlling use of these substances since HR individuals were likely to also use other substances (e.g., opiates and cocaine) to compensate (Shaffer, LaPlante et al. 2004, Copersino, Boyd et al. 2006, Peters et Hughes 2010). Inversely, substance users in harm reduction settings reported more time spent in activities needed to obtain or use tobacco, probably due to more socio-economic difficulties (Ross, Teesson et al. 2005, Moracchini, Frauger et al. 2012). The pharmacological adaptation “withdrawal” criterion had lower prevalence for cocaine and cannabis in harm reduction settings, may be due to greater management of withdrawal symptoms through the use of other substances with similar effects (Shaffer, LaPlante et al. 2004, Copersino, Boyd et al. 2006, Peters et Hughes 2010). Criteria related to consequences of use "Psychological/Physical problems" and "hazardous use" less frequent among HR participants for alcohol and cannabis, may be related to their lower perception compared to the psychological and physical impact of opiate and cocaine use or injection practices. Higher socio-economic difficulties of HR participants could explain the higher prevalence of criteria assessing consequences of loss of control, as social impairment criteria and risky use of tobacco (Martin, Langenbucher et al. 2014).

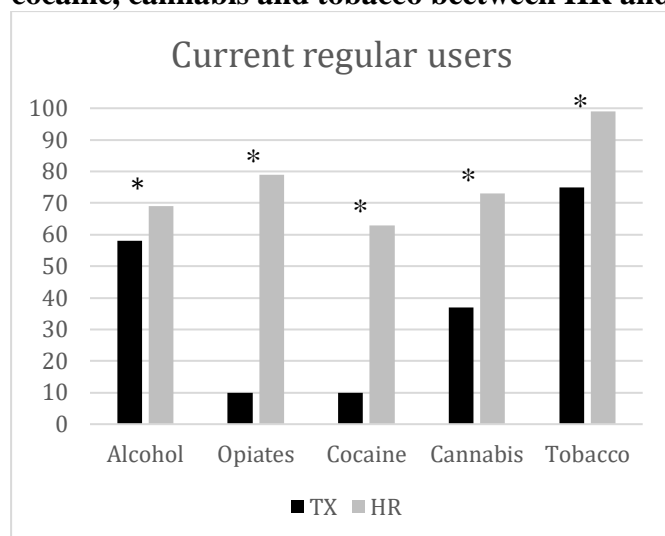
Considering the study of craving as a dimensional phenomenon, these results confirmed that craving is reported by substance users in harm reduction settings (Gu, Wang et al. 2009), and added a significant information on the high level of craving intensity. However, substance users in harm reduction settings reported fewer episodes of craving for cannabis and tobacco in past 30 days than Tx participants. The seeking treatment context seems to be correlated with higher craving frequency. Whether this excess craving frequency contributed to seeking treatment or was a consequence of attempting to reduce use before treatment entry cannot be determined in the frame of this study. As they have less episodes of craving and more current substance use, we suggest that some use could be motivated by self-medication of psychiatric comorbidities and not a compulsive response to craving (Turner, Mota et al. 2018).

Comorbid psychopathology was a possible previously reported factor limiting positive impact of NEP. Among PWID in methadone-treatment, comorbid psychopathology was significantly associated with HIV-transmission-risk behaviors, but the characteristic of the addictive disorder was not explored as a possible other limitation factor (Metzger, Woody et al. 1990, Metzger, Woody et al. 1991). As studies suggested an implication of craving in at-risk practices among HR participants (Kipke, Unger et al. 1997, Kelaher et Ross 1999), and more generally among PWID (Perngmark, Vanichseni et al. 2008), assessment and monitoring craving among NEP participants could improve the efficiency of NEP in reducing the risk of disease transmission.

Study limitations are noted. As with all substance use studies, information is vulnerable to self-report bias. However self-reported substance use tends to be accurate in the absence of sanctions which was the case for this study (Magura, Goldsmith et al. 1987). The sample size of the HR subgroup was smaller than that of the Tx subgroup, and there were important injection practices among HR participants which could explain some differences on use and consequences of use, such as more negative health and social consequences. It will be necessary to confirm these results with a larger sample of HR participants, including substance smokers or people using the nasal route without injection practices.

To conclude, in this study, DSM-5 SUD prevalence was similar among current regular substance users in harm reduction settings or in addiction treatment and all SUD diagnostic criteria were endorsed. However, there were significant differences in some individual criterion prevalence. Further studies are needed to determine if these differences translate a difference of criteria functioning (Shmulewitz, Greene et al. 2015). Interestingly, substance users in HR settings, a use-friendly environment, were as much to experience the craving diagnostic criteria as those seeking treatment.

Figure 1 : Prevalence and comparison of current regular users of alcohol, opiates, cocaine, cannabis and tobacco between HR and Tx participants



Legend: * univariate significantly different.

Table 1 : Comparison of sociodemographics characteristics and polysubstances use between HR and Tx participants.

	HR (n = 130)		Tx (n =1359)		p-value
	N	%	N	%	
Males	99	76.2	914	67.3	.0377
Work in past 30 days	25	19.5	760	56.6	≤.0001*
Level of education 12 years or more cognitive/social	34	26.6	799	59.3	≤.0001*
Poly-addiction	129	99.2	769	56.6	≤.0001*
No main problematic substance use	38	30	0	0	≤.0001*†
	Mean	SD	Mean	SD	p-value
Age	34.2	8.0	38.6	11.5	≤.0001*
Number of SUD diagnosis	3.6	1.0	1.8	0.9	≤.0001*

Legend: *univariate significantly different after FDR adjustment, † non -parametric Fisher test.

Table 2: Comparison of substances used and Substances Use Disorder characteristics for alcohol, cocaine, cannabis and tobacco among current users between HR and Tx participants.

	Alcohol			Cocaine			Cannabis			Tobacco		
	HR	Tx	p-value	HR	Tx	p-value	HR	Tx	p-value	HR	Tx	p-value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Substance users in past 30 days	88 (100)	674 (86)	.0002*	77 (96)	100 (73)	≤.0001*	93 (100)	446 (89)	.0006*	125 (99)	964 (96)	.0352
Main problematic substances	18 (21)	555 (71)	≤.0001*	28 (35)	69 (49)	.0448	3 (3)	273 (54)	≤.0001*	4 (3)	302 (30)	≤.0001*
Current Use Disorder	87 (98)	728 (93)	.0651	76 (93)	133 (94)	.6257	87 (92)	474 (94)	.3652	119 (93)	928 (92)	.5757
Severity of use Disorder												
<i>No diagnosis</i>	2 (2)	59 (8)	≤.0001*	6 (7)	8 (6)	.9246	8 (8)	30 (6)	.0032*	9 (7)	86 (9)	.04810
<i>Mild</i>	15 (17)	60 (8)		8 (10)	17 (12)		14 (15)	56 (11)		14 (11)	157 (16)	
<i>Moderate</i>	15 (17)	122 (16)		9 (11)	15 (9)		27 (28)	78 (16)		44 (35)	334 (33)	
<i>Severe</i>	57 (64)	546 (69)		59 (72)	101 (72)		46 (48)	340 (68)		61 (48)	437 (43)	
Poly-addiction	89 (100)	554 (70)	≤.0001*	81 (99)	127 (90)	.0123*	94 (99)	410 (81)	≤.0001*	127 (99)	701 (69)	≤.0001*
Daily craving episodes	18(21)	153 (21)	.0401	16 (21)	23 (20)	.0283	11 (12)	148 (33)	≤.0001*	37 (30)	380 (39)	.3797
	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value	Mean (SD)	Mean (SD)	p-value
Number of days of substance use in past 30 days	26.3 (7.1)	15.4 (11.7)	≤.0001*	14.0 (10.7)	5.3 (7.7)	≤.0001*	23.9 (8.8)	20.2 (12.1)	.0007*	29.4 (3.7)	27.0 (8.3)	≤.0001*
Number of years of regular use	14.7 (7.9)	14.3 (10.6)	.6871	6.3 (6.6)	4.3 (4.6)	.0165*	18.0 (8.3)	13.8 (8.9)	≤.0001*	19.5 (8.0)	20.0 (10.5)	.5081
Number of craving days	18.0 (11.8)	16.5 (11.3)	.0660	15.6 (11.2)	15.2 (11.0)	.0189	12.4 (12.0)	19.4 (11.7)	≤.0001*	16.9 (12.4)	22.8 (11.1)	≤.0001*
Maximum intensity of craving	8.4 (1.6)	8.1 (1.9)	.7223	8.5 (1.7)	8.5 (1.8)	.4818	8.3 (1.8)	8.2 (2.0)	.6493	8.4 (1.6)	8.3 (2.0)	.8047
Mean intensity of craving	6.9 (2.5)	6.3 (2.1)	.1676	6.6 (2.3)	6.6 (2.0)	.5842	6.6 (2.5)	6.3 (2.1)	.5790	6.5 (2.5)	6.7 (2.2)	.5001

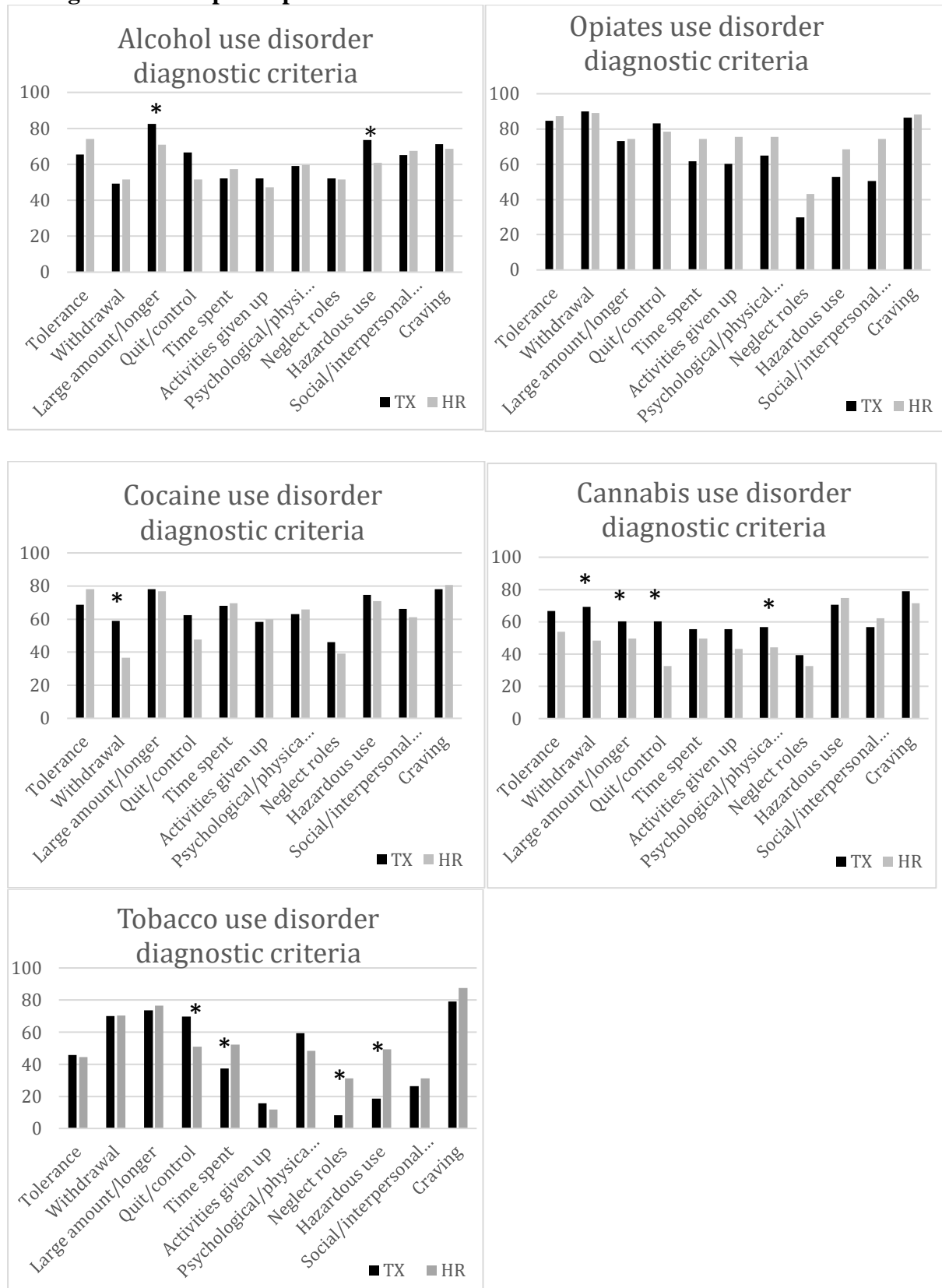
Legend: * significant difference (FDR adjusted); model adjusted on age, gender, level of education, poly-addiction and number of days of substance use in past 30 days.

Table 3: Comparison of Substances used and Opiates Use Disorder characteristics among current users between HR and Tx participants.

	Opiates		
	HR	Tx	p-value
	N (%)	N (%)	
At least one opiates users in past 30 days	99 (99)	117 (91)	.0071*
Heroin	31 (30)	23 (18)	.0284
Methadone	40 (40)	29 (23)	.0042*
Buprenorphine	35 (34)	50 (36)	.5152
Opioid agonist treatment prescribed	48 (48)	53 (41)	.3045
Other opiates	70 (67)	46 (35)	≤.0001*
More than 1 opiate	52 (53)	27 (27)	.0003*
Opiates as main problematic substances	50 (49)	89 (69)	.0027*
Current OUD	102 (100)	128 (98)	.1240
OUD severity			
<i>No diagnosis</i>	0	3 (2)	.0956†
<i>Mild</i>	1 (1)	7 (5)	
<i>Moderate</i>	15 (15)	23 (18)	
<i>Severe</i>	86 (84)	98 (75)	
Poly-addiction	102 (100)	100 (76)	≤.0001*
Daily opiates craving	17 (17)	40 (35)	.0076*
	Mean (SD)	Mean (SD)	p-value
Number of days of use in past 30 days			
Heroin	2.6 (6.3)	2.3 (7.1)	.7780
Methadone	9.6 (13.5)	4.2 (9.8)	.0009*
Buprenorphine	8.0 (12.7)	10.1 (13.9)	.2219
Other opiates	12.0 (12.8)	8.2 (12.8)	.0241
Number of years of regular use			
Heroin	6.1 (5.2)	2.9 (4.2)	<.0001*
Methadone	2.2 (3.4)	0.7 (1.8)	.0002*
Buprenorphine	4.0 (5.2)	3.3 (5.2)	.3199
Other opiates	2.6 (3.9)	2.3 (4.0)	.5160
Number of craving days	14.8 (11.8)	21.7 (11.0)	.0775
Maximum intensity of Opiates craving	8.5 (1.7)	8.5 (1.8)	.6426
Mean intensity of Opiates craving	6.2 (2.3)	6.8 (2.3)	.6891

Legend: † non -parametric Fisher test; * significant difference (FDR adjusted); ◊ model adjusted on age, gender, level of education, poly-addiction and number of days of heroin, methadone, buprenorphine and other opiates use in past 30 days.

Figure 3: Prevalence of SUD criteria for alcohol, opiates, cocaine and tobacco among HR and Tx participants.



Legend: * significantly different for criteria model adjusted on age, gender, level of education, poly-addiction and number of current substance use years.

Table 4: Significant prevalence differences of SUD criteria for alcohol, opiates, cocaine, cannabis and tobacco among HR and Tx participants.

	Criteria	Alcohol		Opiates		Cocaine		Cannabis		Tobacco	
		Tx	HR	Tx	HR	Tx	HR	Tx	HR	Tx	HR
Loss of control	Large amount/longer	+	-					+	-		
	Quit/Control							+	-	+	-
	Time spent									-	+
	Craving										
Social Impairment	Activities given up										
	Neglect role									-	+
	Social/interpersonal problems										
Risky use	Hazardous use	+	-							-	+
	Psychological/Physical problems							+	-		
Pharmacological adaptation	Tolerance										
	Withdrawal					+	-	+	-		

This table shows the criteria with significant prevalence difference and the meaning of these differences for each criterion and substance explored. The "+" indicates the subgroup with higher frequency of criteria than the "-" subgroup. For example, the cannabis "difficulty to quit or control" criterion was more frequently endorsed in the Tx subgroup.

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**Manuscript 5: Do DSM-5 substance use disorder criteria differ by user care settings?
An Item Response Theory analyses approach.**

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Keywords: Item Response Theory Analysis, Substance use disorder, Craving, Harm Reduction Center, patient seeking treatment.

ABSTRACT

Aim: To examine the psychometric characteristics of diagnostic criteria for Substance Use Disorders (SUD) between substance users in harm reduction settings (HR) and substance users seeking treatment (Tx).

Methods: Differential Item and Test Functioning (DIF & DTF) analysis were performed to examine differences in the difficulty of endorsement of the 11 diagnostic criteria and to test if the criteria set as a whole (the “test”) functioned differently by care settings (Tx vs. HR). To test DIF, multiple indicator multiple cause (MIMIC) structural equation models were used.

Results: Regardless of the substance, “craving”, “large amount”, “time spent”, “tolerance” and “activities given up” criteria had similar functioning by care settings. Little evidence for DIF was found for other criteria. The criteria set as a whole did not function differently by care settings for alcohol, cocaine and tobacco. For cannabis, compared to HR, the Tx subgroup had a greater number of endorsed criteria. For opiates, compared to HR, the Tx subgroup had a smaller number of endorsed criteria with the same trait severity than Tx subgroup.

Conclusion: The unidimensionality of the 11 DSM-5 criteria and applicability of all criteria and diagnosis was confirmed in this large sample of problematic substance users. While the majority of the loss of control criteria functioned well in both care settings, the criteria related to consequences of substance use had several differential functioning.

Keyword: DSM-5; diagnostic criteria; Substance use disorder; craving; differential item functioning;

INTRODUCTION

Substance use disorders have a variety of negative consequences, and are responsible for substantial morbidity and mortality worldwide (Degenhardt et al., 2018). Recent changes to Substance Use Disorder (SUD) diagnosis in the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) included deleting the legal problem criterion, merging the remaining abuse criteria with dependence criteria and adding craving as a new criterion, for a set of 11 criteria to diagnose SUD (American Psychiatric Association, 2013; Auriacombe et al., 2018; Hasin et al., 2013). The unidimensionality and the psychometric validity of the 11 DSM-5 SUD criteria were observed across substances in general population and clinical samples, worldwide (Castaldelli-Maia et al., 2015; Hagman, 2017; Hasin et al., 2013; Kervran et al., 2019b; Serier et al., 2019; Shmulewitz et al., 2015). The structural validity of the 11 DSM-5 alcohol, cannabis, cocaine and heroin criteria as latent constructs was observed in clinical samples from various types of addiction treatment settings, where the clinical outcomes were substance use reduction or abstinence (Hasin et al., 2012; Serier et al., 2019).

Another element of validity is whether items or item sets function differently across population subgroups. Differential item functioning (DIF) occurs if a criterion does not have the same relationship to a latent variable across subgroups (Embretson and Reise, 2000) (Derringer et al., 2013; Hasin et al., 2013; Shmulewitz et al., 2015). Criteria with DIF may not work the same way in specific groups (Shmulewitz et al., 2015). If enough items function differently in a set, this can lead to differential test functioning (DTF), which means that specific groups are more likely to get a diagnosis because they are more likely to endorse some criteria (Shmulewitz et al., 2015). Previous studies in clinical samples have found DIF and DTF by sociodemographic and psychiatric disorders (Hasin et al., 2012; Kervran et al., 2019b). However, no studies have compared DIF and DTF between samples of substance users from different care settings, notably users who sought treatment to stop their substance use as compared to users in harm-reduction setting.

A substance user attempting to abstain in addiction treatment setting may have different characteristics and expectations than a substance user in harm reduction (HR) setting. HR program participants are substance users seeking support for safer use to decrease consequences of their substance use, while not abstaining from use (Des Jarlais, 1995; Hawk et al., 2017). The prevalence of SUD is high among substance users in HR setting (Kidorf et al., 2004), but they may have less loss of control of use and are diagnosed on the consequences of their regular use, which brings them to the HR setting rather than treatment of the addictive disorder. No studies have reported on the prevalence and distribution of each diagnostic criterion among HR participants (Kervran et al., 2018). Inversely, criteria could be specific to substances users in treatment settings (Kessler et al., 2001), as strong desire to quit use (Serier et al., 2019), or

craving often described as particularly prevalent among people trying to stop, or abstinent (Cummings et al., 1985; Shiffman et al., 1986).

At the same SUD latent trait severity, diagnostic criteria that are related to consequences of substance use may be more frequent among substance users in HR setting than among substance users seeking addiction treatment. If this were the case, such criteria might function differently, which is important to determine. Thus, this study examined the psychometric properties of the 11 DSM-5 SUD diagnostic criteria for alcohol, opiates, cocaine, cannabis and tobacco in a large community sample of substance users, comparing substance users in harm reduction setting and substance users in outpatient addiction treatment setting.

METHODS

Participants and study design

Participants were selected from two cohort studies, the Addiction Aquitaine cohort (ADDICTAQUI) (Auriacombe, Accessed september 2019) and the COhort to identify Structural and INdividual factors associated with drug USE (COSINUS) (Auriacombe et al., 2019). Participants seeking addiction treatment (Tx) from the ADDICTAQUI cohort were recruited at their entry into outpatient addiction clinics if they met criteria for a DSM-5 substance use disorder for at least one substance (Auriacombe, Accessed september 2019). Participants seeking support for safer use in harm reduction settings (HR) from the COSINUS cohort were regular users of illegal substances who had injected at least once during the past month (Auriacombe et al., 2019). The common inclusion criteria for the two samples were: over 18 years old, French-speaking, current regular users of at least one substance (alcohol, cocaine, tobacco, opiates, cannabis) and provided documented informed consent. Participants were considered current users if they used the substance at least 2 times per week for 12 months. Both cohorts were approved by French Regulation and ethical committee (CNIL, CPP, CEEI/IRB) (Auriacombe, Accessed september 2019; Auriacombe et al., 2019).

Measures

Each subject completed a baseline interview that included a standardized and structured interview, administered by trained interviewers.

Sociodemographic variables

Sociodemographic variables (age, gender, level of education) were collected with the Addiction Severity Index (ASI) (Denis et al., 2016; McLellan et al., 1992).

Substance use disorder

Substance use-related variables were collected with the ASI. Among current regular users, for each substance, each of the 11 DSM-5 SUD criteria (American Psychiatric Association, 2013) was evaluated for the past 12 months, with a guided structured interview. Polyaddiction was defined as individuals who met more than one current SUD.

Analyses

For each substance, analyses were conducted separately among current regular users: 876 alcohol users (Tx n= 787, HR n=89), 233 opiates users (Tx n= 131, HR n=102), 223 cocaine users (Tx n= 141, HR n=82), 599 cannabis users (Tx n= 504, HR n=95) and 1,142 tobacco users (Tx n= 1014, HR n=128). The majority of the sample was from the ADDICTAQUI cohort, for which the unidimensionality and psychometric validity of the 11 SUD DSM-5 criteria was previously reported (Kervran et al., 2019b). In this paper, the HR subgroup (COSINUS) was added to the previously studied Tx subgroup.

Unidimensionality and Item Response Theory (IRT) models

For each substance, a one-factor confirmatory factor analysis (CFA) model of the 11 SUD criteria confirmed unidimensionality when the model showed adequate fit, based on comparative fit index (CFI) ≥ 0.95 or Tucker-Lewis index (TLI) ≥ 0.95 and RMSEA (smaller values indicate better fit) ≤ 0.06 (Hu and Bentler, 1999). Then, a 2-parameter logistic IRT model was estimated, to examine each criterion's difficulty to be endorsed (inversely related to frequency) and discrimination (how well the criterion differentiated between respondents with high and low severity of the latent trait) (Embretson and Reise, 2000; Hasin et al., 2012; Shmulewitz et al., 2011).

Differential Item Functioning (DIF)

For each substance, Differential Item (criterion) Functioning analysis was carried out using multiple indicator multiple cause (MIMIC) structural equation models (Jones, 2006; Kline, 2011a, b; Woods et al., 2009), allowing examination of uniform DIF. A strength of the MIMIC model is its ability to examine and to adjust the impact of DIF during analyses, as well as the ability to examine multiple group variables simultaneously, allowing control for several covariables (Teresi and Fleishman, 2007). The relatively small sample size for the HR subgroup led to the choice of MIMIC modeling (Jones, 2006; Kline, 2011a, b; Woods et al., 2009). Each criteria set was modeled as a latent variable indicated by the 11 criteria and regressed on care settings (i.e., Tx vs HR), while adjusting for age, gender, years of regular substance use (dichotomized by the median in each group), level of education (>12 years vs. <12 years) and poly-addiction. DIF is indicated when a criterion shows a statistically significant association

with care setting, after accounting for the association with the latent variable. This independent association (between the criterion and the care settings) is indicated by statistically significant modification indices (MI), which suggest that adding that association to the model would improve model fit. If DIF was indicated, we determined which care settings (Tx or HR subgroup) showed higher probability of endorsement of the criterion at the mean of the latent trait. To adjust for multiple testing of the 11 criteria, we used Bonferroni adjustment, considering a result significant at $p=0.05/11=0.0045$ (≤ 0.005). All IRT analysis were conducted in Mplus 8 (Muthen and Muthen, 1998-2017).

Differential Test Functioning (DTF)

For each substance, we examined DTF by care settings (Tx vs. HR) (Morales et al., 2006; Raju et al., 1995). We used R code (R Core Team, 2018) to calculate the average difference in the expected number of criteria for individuals with the same trait severity in each treatment environment (Shmulewitz et al., 2011). A difference of <1 expected number of criteria by subgroup indicates no DTF, as differences that small should lead to minimal differential diagnosis of SUD by care settings.

RESULTS

Sample Description

The majority of the individuals were males (68%), the mean age was 38 years, and 56% had a high level of education (≥ 12 years) (Table 1). The large majority of regular users met SUD diagnosis (alcohol 93%, opiates 98%, cocaine 92%, cannabis 92% and tobacco 89%). More than half (66%) had a poly-addiction, with a majority in the HR subgroup. The endorsement rate to each of the DSM-5 criterion was high for alcohol, opiates, cocaine, cannabis, and more variable for tobacco (10.9% to 80.0%) (Table 2).

Dimensionality & IRT

For alcohol, opiates, cocaine and cannabis, unidimensionality was confirmed by the model fit indices (Table 2). For tobacco, unidimensionality was confirmed by RMSEA, but TLI and CFI were slightly below the recommended 0.95. Across all substances, discrimination parameters ranged from 0.57 to 2.38, indicating that criteria had relatively high ability to delineate individuals who were higher vs. lower on the latent trait, and the difficulty estimates of ≤ 0.0 indicated that even subjects below average on the latent trait had at least a 50% probability of endorsing the criterion. IRT analysis indicated that for each substance, the 11 items were spread across the severity continuum, with "craving" showing high discrimination and "hazardous use" showing low discrimination (Figure 1).

Differential Item Functioning

DIF analyses (Table 3) indicated that for all substances, the “craving”, “large amount”, “time spent”, “tolerance” and “activities given up” criteria showed no significant DIF, and, for alcohol and opiates, all criteria showed no significant DIF.

For cocaine, the “withdrawal” criterion was significantly ($p=.001$) more likely to be endorsed in Tx subgroup than HR subgroup. For cannabis, the “quit/control” criterion was significantly ($p=.004$) more likely to be endorsed in Tx subgroup than HR subgroup, while the “social problems” criterion was significantly ($p=.004$) less likely to be endorsed in Tx subgroup than HR. For tobacco, the “quit/control” and “psychological/physiological” problems criteria were significantly ($p<.001$ and $p=.004$ respectively) more likely to be endorsed in Tx subgroup than HR subgroup, while the “neglect role” and “hazardous use” criteria were significantly ($p<.001$) less likely to be endorsed in Tx subgroup than HR.

Differential Test Functioning (DTF (Figure 2))

For the total criterion set, the average expected difference in number of criteria endorsed between the two care setting subgroups was <1 for alcohol (0.39), cocaine (0.39) and tobacco (0.51). For cannabis, the difference was 1.16, with the Tx subgroup endorsing a greater number of criteria than the HR subgroup at the same trait severity. For opiates, the difference was 1.09, with the HR subgroup endorsing more criteria than the Tx subgroup at the same trait severity.

DISCUSSION

This is the first study to examine differential item and test functioning of DSM-5 SUD criteria between substance users accessing treatment (Tx) and substance users in harm reduction settings (HR). Across all substances (alcohol, cannabis, cocaine, opiates, and tobacco), the majority of the criteria had similar functioning regardless of the care settings. For cannabis and opiates, the criteria set as a whole functioned differently by care settings.

Consistent with prior studies, unidimensionality was confirmed for alcohol, opiates, cocaine and cannabis, further supporting the DSM-5 changes (Hasin et al., 2012; Hasin et al., 2013; Kervran et al., 2019b). For tobacco, unidimensionality was equivocal, perhaps due to the former DSM-IV abuse criteria, which showed low factor loadings and DIF, suggesting their limitations as indicators of the construct, as operationalized in this study (Kervran et al., 2019b).

From the loss of control dimension of SUD (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018), the “craving”, “using in larger amount than intended” and “time spent to use” criteria had similar functioning across care settings. For cannabis and tobacco, the “difficulty to quit or control” criterion was more frequently endorsed in the treatment setting subgroup, likely because these subjects were asking for help to change their use. Substance users in harm reduction settings could be either more interested in reducing harm than controlling cannabis or tobacco use, or they could have been more successful in controlling use of those substances since such individuals were likely to also use other substances (e.g., opiates and cocaine) to compensate (Copersino et al., 2006; Peters and Hughes, 2010; Shaffer et al., 2004).

Of the pharmacological adaptation criteria, substance users seeking addiction treatment endorsed "withdrawal" significantly more frequently than substance users in harm reduction settings. This could be because subjects in treatment setting may attempt to reduce use even before treatment access, and may experience more withdrawal as a consequence than substance users in HR settings who are not necessarily attempting to reduce use (Kervran et al., 2019a; Moracchini et al., 2012).

Of the consequences of use criteria, those related to social impairment and risky use, which tend to be contextually and culturally bound (Auriacombe et al., 2018; Martin et al., 2014) , functioned differently by care settings. The HR subgroup was more likely to endorse “social/interpersonal problem due to use” for cannabis and “neglect roles because of use” and “hazardous use” for tobacco, perhaps due to socio-economic difficulties, often related to substance use or dealing activities that are more frequent among substance users in HR than for those in treatment (Kervran et al., 2019a; Moracchini et al., 2012). For tobacco, “psychological/physiological problems because of use” criterion was more frequently endorsed by substance users in treatment setting, possibly because this group was more aware of such damage caused by tobacco use.

There were no criteria with consistent differential functioning by care settings across all substances.

Overall, alcohol, tobacco and cocaine SUD was expected to be unaffected by the care setting, as the expected number of criteria endorsed was quite similar for those in harm reduction and treatment settings. Although for tobacco, four criteria showed DIF, these balanced out, since two criteria were more frequent in one subgroup and two were more frequent in the other subgroup. For opioids, no individual criteria had a significant DIF, but insignificant functional differences of several criteria, when taken together, were added to give

a significant DTF. Substance users in treatment setting endorsed a greater number of cannabis criteria, perhaps driven by the increased likelihood of endorsing the “difficulty to quit or control” criterion. Future studies should determine exact causes of the DTF.

Study limitations are acknowledged. Sample size for the HR subgroup was small for some substances. A larger sample would give more precise estimates and greater ability to detect differences. The MIMIC model is the recommended method for small sample sizes (as in HR group), but this method does not allow reliable assessment of non-uniform DIF (differences in item discrimination) (Woods et al., 2009). In a previous study among the substance user treatment seeking subgroup, DIF and DTF by psychiatric comorbidities were found (Kervran et al., 2019b). Since substance users in treatment setting showed more severe mental health disability than substance users in HR settings (Compton et al., 2007; Kidorf et al., 2004; Kidorf et al., 2010; Metzger et al., 1990; Ross et al., 2002), future studies should explore if psychiatric comorbidities in the treatment subgroup could explain the DIF and DTF observed.

In conclusion, the present study in a large sample of substance users in different care settings supported the unidimensionality of the 11 DSM-5 criteria and applicability of all criteria and diagnosis. While the majority of the loss of control criteria, the core feature of addiction (American Psychiatric Association, 2013; Auriacombe et al., 2018; Hasin et al., 2013; Martin et al., 2014), functioned well in the different care settings, the criteria related to consequences of use had several instances of differential functioning. Future studies should further explore if the current set of 11 criteria could be simplified to less criteria more focused on those related to the direct expression of loss of control without losing any of the current psychometric quality.

Table 1: Sociodemographic and addiction severity variables in a substance using sample, by substance and care setting.

	Total sample		Alcohol (n=876)		Opiates (n=233)		Cocaine (n=223)		Cannabis (n=599)		Tobacco (n=1142)	
	HR	Tx	HR	Tx	HR	Tx	HR	Tx	HR	Tx	HR	Tx
Age – Mean (SD)	34.2(8)	38.6 (12)	34.9(8.1)	40.3(11.6)	33.6(7.9)	34.3(9.7)	34.2(7.8)	32.8(7.8)	35.2(8.1)	33.5(9.6)	34.1(7.8)	38.3(11.3)
Males – n (%)	99 (76.2)	914 (67.3)	74(83.2)	569(72,3)	79(77.5)	89(67.9)	63(76.8)	115(81.6)	75(79.0)	398(79.0)	97(75.8)	660(65.1)
Level of education ≥ 12 years – n (%)	34 (26.6)	799 (59.3)	21(23.9)	471(60.5)	32(32°)	58(44.6)	16(19.5)	69(48.9)	22(23.7)	242(48.2)	34(27.0)	609(60.4)
Number of years of regular use – Mean (SD)	-	-	14.7 (7.9)	14.3 (10.6)	6.3(4.8)	5.1(4.5)	6.3 (6.6)	4.3 (4.6)	18.0 (8.3)	13.8 (8.9)	19.5 (8.0)	20.0 (10.5)
Mean number of use days in the last 30 days	-	-	26.3 (7.1)	15.4 (11.7)	19.8(12.1)	21(11.8)	14.0 (10.7)	5.3 (7.7)	23.9 (8.8)	20.2 (12.1)	29.4 (3.7)	27.0 (8.3)
Poly-addiction – n (%)	129 (99.2)	769 (56.6)	89(100)	554(70.4)	102(100)	100(76.3)	81(98.8)	127(90.1)	94(99.0)	410(81.4)	127(99.2)	701(69.1)
DSM-5 criteria												
No. endorsed SUD criteria – Mean (SD)	-	-	6.6 (2.8)	6.9 (3.0)	8.3 (2.2)	7.4 (2.6)	7.2 (3.1)	7.2 (3.2)	5.6 (2.8)	6.7 (2.9)	5.5 (2.3)	5.0 (2.5)
SUD diagnosis – n (%)			87 (98)	728 (93)	102 (100)	128 (98)	76 (93)	133 (94)	87 (92)	474 (94)	119 (93)	928 (92)

S.D.: Standard Deviation; HR: substance users in harm reduction setting; Tx: substance users in treatment setting.

Table 2: Parameter estimates from Confirmatory factor analysis 1-factor model, by substance.

	Alcohol (n=876)		Opiates (N=233)		Cocaine (n=223)		Cannabis (n=599)		Tobacco (n=1142)	
	factor loading	Prevalence (%)	factor loading	Prevalence (%)	factor loading	Prevalence (%)	factor model loading	Prevalence (%)	factor loading	Prevalence (%)
Tolerance	0.613	66.2	0.601	85.8	0.690	72.2	0.636	64.6	0.645	45.6
Withdrawal	0.731	49.5	0.678	89.7	0.673	50.7	0.741	65.8	0.697	70.1
Large amount/longer	0.469	81.3	0.586	73.8	0.736	77.6	0.647	58.4	0.568	73.9
Quit/control	0.707	65.1	0.566	81.1	0.667	57.0	0.627	55.9	0.498	67.6
Time spent	0.629	52.5	0.662	67.4	0.793	68.6	0.615	54.4	0.593	39.0
Activities given up	0.782	51.6	0.778	67.0	0.794	58.7	0.646	53.4	0.579	15.1
Psychological/physical problems	0.673	59.1	0.553	69.5	0.815	64.1	0.623	54.8	0.448	58.2
Neglect roles	0.603	51.9	0.739	35.6	0.680	43.5	0.529	38.2	0.484	10.9
Hazardous use	0.380	72.1	0.421	59.7	0.478	73.1	0.328	71.3	0.354	22.2
Social/interpersonal problems	0.735	65.3	0.573	60.9	0.689	64.1	0.589	57.4	0.410	26.9
Craving	0.825	70.9	0.699	87.1	0.826	78.9	0.789	77.8	0.780	80.0
Model fit indices										
CFI	0.967		0.954		0.980		0.970		0.919	
TLI	0.958		0.942		0.975		0.962		0.899	
RMSEA	0.053		0.048		0.048		0.045		0.055	

CFI: Comparative Fit Index, TLI: Tucker Lewis Index, RMSEA: Root Mean Square error of approximation

Figure 1: Item characteristic curves from IRT models of alcohol, opiates, cocaine, cannabis and tobacco DSM-5 use disorder

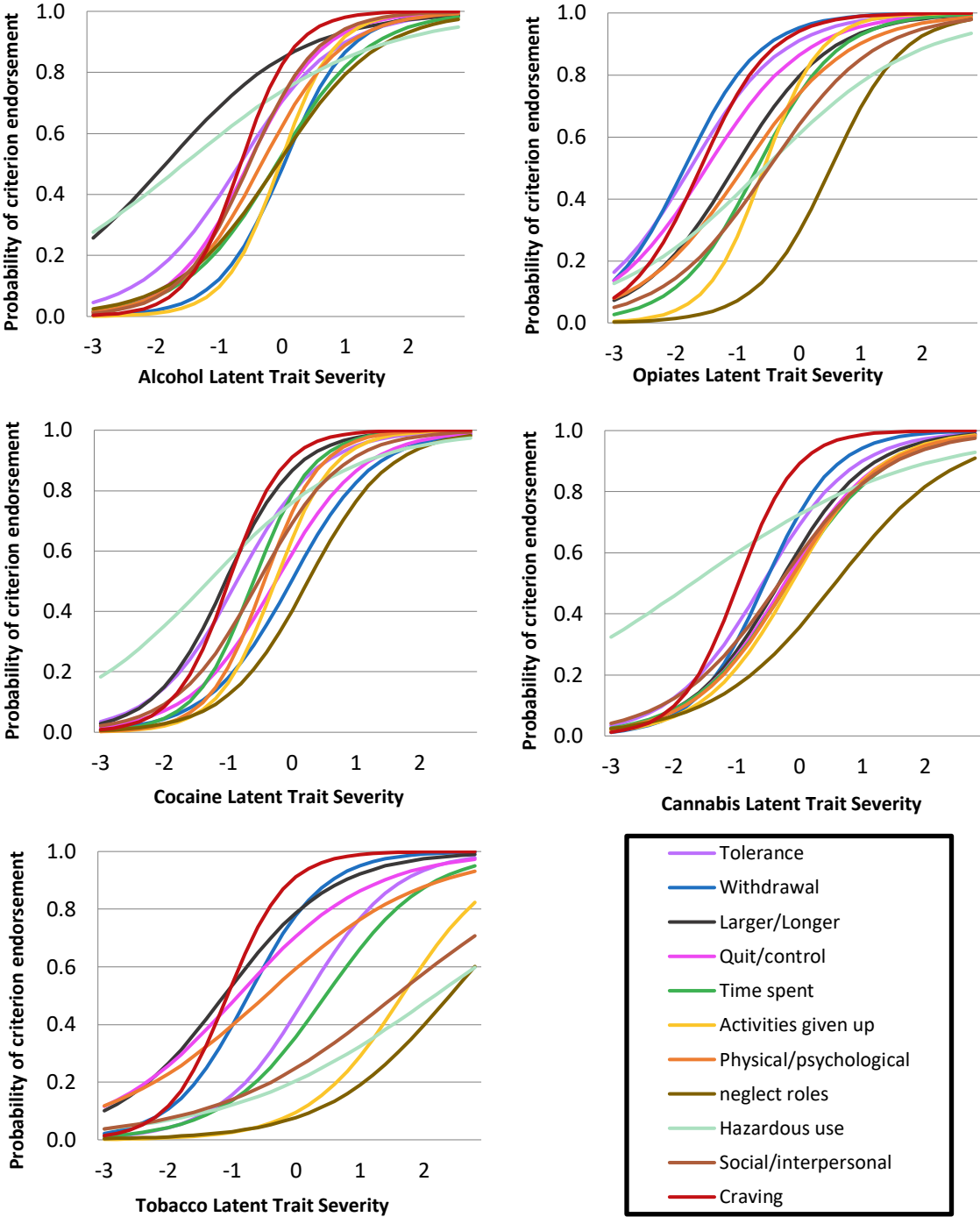
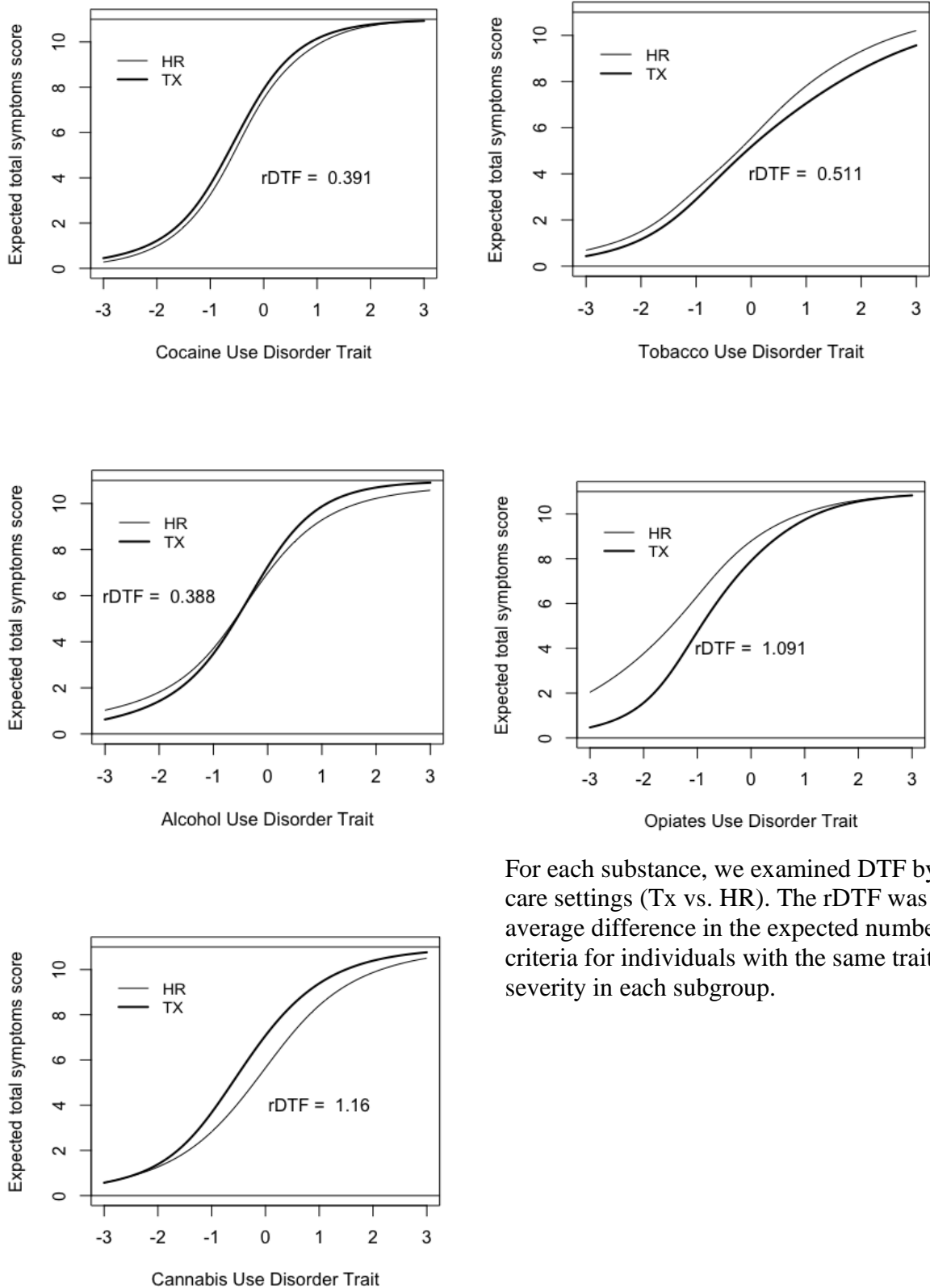


Table 3: Differential Item Functioning (DIF) resume

	Criteria	Tx	HR
Loss of control	Large amount/longer	No DIF	
	Quit/Control	Cannabis & Tobacco +	-
	Time spent	No DIF	
	Craving	No DIF	
Social Impairment	Activities given up	No DIF	
	Social/interpersonal problems	-	+
	Neglect role	Tobacco -	+
Risky use	Hazardous use	Tobacco -	+
	Psychological/Physical problems	Tobacco +	-
Pharmacological adaptation	Tolerance	No DIF	
	Withdrawal	Cocaine +	-

HR: substance users in harm reduction setting; Tx: substance users in treatment setting. This table shows the criteria with DIF and the meaning of these DIF for each criterion and substance explored. The "+" indicates the subgroup with higher frequency of criteria than the "-" subgroup. For example, the cannabis and tobacco "difficulty to quit or control" criterion was more frequently endorsed in the Tx subgroup.

Figure 2: Differential Test functioning by care settings.



For each substance, we examined DTF by care settings (Tx vs. HR). The rDTF was the average difference in the expected number of criteria for individuals with the same trait severity in each subgroup.

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PARTIE III : La valeur prédictive du *craving* sur l'usage

Manuscript 6: How much does craving contribute to use among substance users not attempting to abstain? Preliminary findings from an ongoing Ecological Momentary Assessment Study in substance users in harm reduction programs.

Manuscript in progress (study ongoing)

ABSTRACT

Aims

The main objective of this study was to examine the prospective link between cues, craving and substance use among substance users recruited in harm reduction programs, an environment that is substance-use-friendly.

Methods

Ecological momentary assessment was used during a 2-week period. Setting Data were collected in a French harm reduction setting. Substance users with sedatives or stimulant addiction were included. Using mobile technologies, participants were questioned four times per day relative to craving, substance use and exposure to either substance-specific cues (e.g. seeing a syringe) or personal cues unique to that individual (e.g. seeing the specific person with whom the substance is used). Hierarchical linear and nonlinear modelling was used to test the prospective link between cues, craving and substance use.

Results

Nineteen subjects were included at this stage of the study out of the 40 planned. As the day of the study progressed, no significant change was observed in the intensity of craving ($t=0.360$, $p=0.723$), and the frequency of substance use ($t=-0.313$, $p=0.758$). The number of cues experienced at any given assessment (T0) was not associated with craving intensity at the next assessment. Craving was associated strongly with concurrent substance use ($t=3.993$, $p<0.001$), and remained a significant predictor ($t=2.332$, $p=0.032$) of substance use up to four hours later on average. Substance use was a strong significant predictor of craving intensity at the next assessment ($t=4.386$, $p<0.001$). When the models were adjusted for age and gender, or on status on the dependent variable at T0, only the prospective value of substance use on craving intensity remained significant.

Discussion

The preliminary results show for the first time, in HR setting, that active substance users, increase of craving intensity predicts increase in probability of main problematic substance use. In addition, our results highlight a bidirectional nature of the craving and substance use

association, because substance use is a strong predictor of increase of craving intensity. In this way, the findings underscore the extent to which craving contribute to addiction chronicity even in context of active use. The study needs to be continued because some results could be due to a lack of power and are likely to become significant with more inclusions.

INTRODUCTION

Substance use disorders are one of the most important contributors to the global burden of disease (Degenhardt, Charlson et al. 2018) making addiction a worldwide public health issue. Addiction is characterized by loss of control of use, relapse, and craving (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018). Craving is defined as an intense desire or urge to use and/or an occurrence of obsessive thoughts about the object of addiction, and was added recently as a new diagnostic criterion for Substance use Disorder (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2016, Auriacombe, Serre et al. 2018). Craving is a dynamic phenomenon that can show rapid variations during the same day and is responsive to changes in the environment (Drummond, Litten et al. 2000, Tiffany, Warthen et al. 2008, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015). In clinical research, it has been shown that craving increases in response to exposure to stimuli or "cues" that are generally associated with substance use, including substance-specific cues such as bottles, syringes or lighters or person-specific cues such as "being with my friend Sam" or "seeing my green plastic box" (O'Brien, Childress et al. 1998, Carter and Tiffany 1999, Yu, Zhang et al. 2007, Childress, Ehrman et al. 2008, Fatseas, Denis et al. 2011). The application of mobile technologies, such as Ecological Momentary Assessment (EMA), allow for the investigation of cue exposure and craving fluctuations in real-time and in the natural contexts of daily life (Swendsen and Salamon 2012). Many studies using EMA have shown a prospective link between cue exposure, craving and substances use (Hopper, Su et al. 2006, Epstein, Willner-Reid et al. 2009, Moore, Seavey et al. 2014, Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Sayette 2016) (Singh and Björling 2019), and a study proposed a "cues-craving-use" model of addiction (Fatseas, Serre et al. 2015, Auriacombe, Serre et al. 2018). In this model, craving was a strong predictor of substance use after exposition to cues previously associated to the substances used (Fatseas, Serre et al. 2015). However, all findings should be interpreted relative to individuals seeking treatment. A subject in treatment who is attempting to abstain, may be faced to very different characteristics and expectations than a user not in treatment (Drummond, Litten et al. 2000). Hence, it is possible that the "cues-craving-use" model of addiction could be, at least partly, induced by the context of treatment, because users are attempting to reduce or stop substance use due to external factors (Musalek 2013). It therefore is of interest to determine if the prospective link between cues, craving and substance use is found in active substance users in a substance-use-friendly environment such as Harm Reduction (HR) programs.

Participants of harm reduction programs have significant probability of having a substance use disorder, are engaged in use and are accessible to research. Harm reduction

programs, including Needle Exchange Programs (NEP), were adopted in many countries to face the HIV epidemic among people who inject drugs (PWID) (Gibson, Flynn et al. 2001, Moatti, Vlahov et al. 2001, Fatseas, Denis et al. 2012, Degenhardt, Peacock et al. 2017). In the harm reduction perspective abstinence is not essential to reducing harm (Little, Hodari et al. 2008). Its interventions aim to reduce the harm that substance use causes to individuals without necessarily reducing substance use (Des Jarlais 1995, Marlatt 1996, Little, Hodari et al. 2008, Hawk, Coulter et al. 2017). Only very few studies assessed craving among HR participants, but they showed that it was reported (Gu, Wang et al. 2009, Kervran, Serre et al. 2019) . Some EMA studies explored craving and/or substance use among substance users recruited from HR settings but none tested the prospective link between cue exposure, craving intensity, substance use and risk practices (Kirk, Linas et al. 2013, Linas, Latkin et al. 2015, Roth, Rossi et al. 2017, Mackesy-Amiti and Boodram 2018).

The main objective of this study was to examine the prospective link between cues, craving and substance use among substance users recruited in harm reduction programs, an environment that is substance-use-friendly.

METHODS

Participants

Subjects were recruited in a harm reduction program in Bordeaux, France, and were eligible for inclusion if they had a current substance use, injected or smoked substances at least once in the past 30 days, met DSM-5 substance use disorder criteria for stimulants (amphetamine, cocaine, methylphenidate, cathinone), opiates (heroin, buprenorphine, morphine) or other sedative substances, were 18 years of age or more, and did not demonstrate active psychosis or severe cognitive impairment. The local research and ethics committees approved this study based on local and international regulations for human research. After complete description of the study to the subjects, written informed consent was obtained.

Procedure

The feasibility and validity of the ambulatory methodology used was demonstrated in samples of substances users in treatment and in HR settings (Serre, Fatseas et al. 2012, Mackesy-Amiti and Boodram 2018). During their visit to the HR program, participants were interviewed by a study interviewer to inform about the study, and screen for inclusion and exclusion criteria, Individuals who gave consent for the study received a one-hour clinical interview to assess addiction severity, psychiatric comorbidity, medical disorders, and social adjustment. A semi-structured interview was conducted to identify their person-specific cues (Fatseas, Serre et al. 2015) that were immediately programmed into the EMA device in addition

to substance-specific cues that were specific to the main problematic substance. After a training session, participants were given a study smartphone for 14 days. Each smartphone was programmed to administer four electronic interviews per day, approximately every 3 hours at random, and took into account the usual awakening time (minimum 10 consecutive hours). Additional urine analysis was conducted. Previous research has found that the validity of self-report information is increased when biological assessments are included in the research protocol (Denis, Fatseas et al. 2012). Financial compensation was provided as a function of number of electronic interviews completed, with a maximum of 100€ for participants completing 75 % or more of electronic assessments.

Variables

Clinical measures

DSM-5 diagnostic criteria for current psychiatric and substance use disorders were assessed using a structured interview that screened for all diagnostic criteria. Substance-related data and sociodemographic data were assessed using a validated French version of the Addiction Severity Index (McLellan, Kushner et al. 1992, Denis, Fatseas et al. 2016). The Interviewer severity Ratings (ISR) from all sections of the ASI were used to assess the severity of the participant's addiction.

Ambulatory monitoring measures

Craving and substance use. At each electronic interview, participants were asked to rate the maximum level of craving (i.e. the desire to use the main problematic substance reported at the first interview) that they felt since the previous assessment on a seven-point scale (1 *no desire* to 7 *extreme desire*). They were also asked if they had used the main problematic substance (yes/no), the quantity uses (number of use) and infection risk practices (at least on risk practices: share and re-use materials) since the previous assessment, followed by questions concerning the use of any other form of psychoactive substance during that time period (tobacco, alcohol, opiates, cocaine, amphetamine, cannabis, or other substances). Single-item scales were used to assess craving as they are advantageous in situations calling for repeated and rapid reporting of craving throughout an experimental paradigm where measurement reactivity can be problematic (Sayette, Shiffman et al. 2000). Repeated assessment can be useful for understanding not just intensity but also duration and peak levels of craving (Sayette, Martin et al. 2005, Sayette 2016).

Substances-specific and Person-specific cues. Following the same procedure as a previous study (Fatseas, Serre et al. 2015), participants were asked at each electronic assessment if they had been in contact with personal and substances-specific cues. Personal cues derived from the participants' personal interview concerning which specific objects,

individuals, circumstances, emotions or environmental contexts were commonly paired with their own substance use. Examples of person-specific cues include "being with my friend Sam", "seeing my green plastic box", or "being in my backyard". Substance-specific cues were also coded among person-specific cues if they addressed a unique or non-generalizable characteristic of the cue (e.g. "The type of glass I like to drink from"). Substance-specific cues was obtained by proposing a list of items reflecting objects or contexts that typically accompany the use of that substance, such as sight or smell of the substance, materials used to consume the substance (e.g. syringe, lighter, bottle), or places paired with substance use (e.g. bar, tobacco vendor).

Statistical Analysis

Hierarchical linear and nonlinear modeling (Raudenbush, Bryk et al. 2005) was used to account for the multilevel structure of the data that involved within-person variance in cues, craving and substance use, as well as between-person variance in clinical and sociodemographic characteristics. The primary objective of examining the association of cues with craving was achieved by random coefficient models that simultaneously included the number of both types of cues encountered at any given assessment (T0) as a predictor of craving levels at the same assessment (T0), or the next assessment (T1, approximately three hours later). The second objective of examining the association of craving with substance use and risk practices was achieved by random coefficient models that simultaneously included the level of craving intensity at any given assessment (T0) as a predictor of substance use (yes/no) and risk practices at the same assessment (T0) and the next assessment (T1). All time-lagged analyses examined within-day (and not across-day) associations (Fatseas, Serre et al. 2015). The γ coefficients generated from these models represent the average within-person association between a predictor (e.g. number of cues) and the outcome (e.g. craving), and the t-ratios are the test statistic values for the null hypotheses that corresponding parameters are equal to zero. Missing data was handled by excluding that particular observation from the analyses. Additional analyses were conducted for adjustment on age and gender; and for the status of the dependent variable at the T0 assessment in prospective analysis

RESULTATS

Nineteen subjects were included at this stage of the study out of the 40 planned. Table 1 provides a description of the clinical characteristics of the sample and information concerning mobile assessment of craving, cue exposure and substance use over the two-week study period. The average response rate with the multiple ambulatory assessments was 74.5 % (30% to 95%).

Polysubstance use was very frequent over this period, with 97% of positive reports involving substances other than the main problematic substance. Use of these additional substances was explained in most cases by cigarette smoking (94% of EMA observations), alcohol use (47%) and cannabis (49%). Among participants in the stimulant group (cocaine, methylphenidate) use of any opiates was reported in 26% of observations. Most observations also included reports of exposure to multiple cues, whether substance-specific or person-specific. As the day of the study progressed (Figure 1), no significant change were observed in the intensity of craving ($\gamma = 0.006$, $SE=0.018$, $t=0.360$, $p=0.723$), the frequency of substance use ($\gamma = -0.006$, $SE=0.020$, $t=-0.313$, $p=0.758$), and the number of substance-specific and person-specific cues ($\gamma = -0.120$, $SE=0.064$, $t=-1.881$, $p=0.076$ and $\gamma = -0.002$, $SE=0.026$, $t=-0.080$, $p=0.937$ respectively).

The intensity of craving was examined next as a function of the number and type of cues. Craving intensity was strongly associated with the number of concurrently substance-specific cues and person-specific cues ($\gamma = 0.133$, $SE=0.027$, $t=4.915$, $p<0.001$ and $\gamma = 0.208$, $SE=0.061$, $t=4.340$, $p<0.001$ respectively). Table 2 demonstrates the prospective associations of cues with craving intensity over subsequent hours of the same day. The number of person-specific cues experienced at any given assessment (T0) was not associated with craving intensity at the T1 assessment occurring on average four hours later. However, the number of substance-specific cues tend to prospectively predicted, but not significantly, craving intensity over this same time period.

The prospective association between craving, main problematic substance use and infectious risk practices is presented in Table 3. Craving assessed at T0 was associated strongly with concurrent substance use ($\gamma = 0.353$, $SE=0.089$, $t=3.993$, $p<0.001$), and remained a significant predictor of T1 substance use up to four hours later on average. Substance use at T0 was also examined as a predictor of T1 craving intensity. Substance use reported at T0 was a strong significant predictor of craving intensity at the next assessment occurring on average four hours later ($\gamma = 0.683$, $SE=0.156$, $t=4.386$, $p<0.001$). Craving assessed at T0 was associated with concurrent infectious risk practices ($\gamma = 0.239$, $SE=0.095$, $t=2.525$, $p=0.021$), but not associated with risk practices at the T1 assessment.

When the models were adjusted for age and gender, or on status on the dependent variable at T0, only the prospective link between substance use at T0 and higher craving intensity at T1 remained significant ($\gamma = 0.838$, $SE=0.276$, $t=3.046$, $p=0.008$ and $\gamma = 0.430$, $SE=0.163$, $t=2.635$, $p=0.017$ respectively)

DISCUSSION

The objective of the present investigation was to test the generalizability of the "cues-craving-use" model among substance users in harm reduction programs, a substance-use-friendly environment. The results were consistent with findings found in substance users in treatment: an increase in exposure to cues tend to predicted an increase of craving intensity which tend to predicted an increase in probability of use of the main problematic substance. In addition, we also found that substance use was a strong predictor of craving intensity increase in the following hours which was not the case for substance users attempting to abstain. These findings underscore the extent to which craving contributes to the persistent use and relapse regardless of treatment access.

Substance users in HR settings are a high-risk population with multiple factors potentially interfering with study participation, such as socioeconomic difficulties (Mackesy-Amiti and Boodram 2018). Nonetheless, the study acceptability was high, as all of the eligible subjects agreed to participate, none withdrew their consent during the study, and 76% initiated EMA assessments. The most common reasons for study dropout were stolen smartphones and drop-out from HR program. Nevertheless, 95% of those who initiated EMA also completed the follow-up interview. As in other EMA studies among individuals with addiction and/or among active substance users in HR, the response rate was high (Serre, Fatseas et al. 2012, Mackesy-Amiti and Boodram 2018).

In contrast to our study among substance users in treatment (Fatseas, Serre et al. 2015), no change was observed in cue exposure, craving intensity and frequency of main substance use during the course of the study. This clearly documents that we were in a stable substance using population not attempting to reduce substance use, consistent with HR perspective (Des Jarlais, Gaist et al. 1995, Marlatt 1996, Little, Hodari et al. 2008, Hawk, Coulter et al. 2017).

The incentive motivation model (Robinson and Berridge 2000) hypothesized that cognitive processes and more particularly attentional bias associated to cue-exposure play a mediating role between stimuli, craving and substance use (Franken 2003). Our previous results among substance users in treatment support this notion as exposure to cues with increased intrinsic salience may produce a hyperattentive state that makes it difficult to draw attention away from such cues, contributing to increased craving and further substance use (Fatseas, Serre et al. 2015). In our previous study, only person-specific cues, but not substance-specific cues, predicted an increase in craving intensity in subsequent assessments, probably due to low

substance use episodes (33% of EMA reports), which limits exposure to substance-specific cues (Fatseas, Serre et al. 2015). In the present study among substance users not attempting to abstain, high frequency of use (51% of EMA reports) resulted in higher exposition to substance-specific cues (mean number of substance-specific cues 2.49 (SD 2.26) in previous study and 7.72 (SD 5.5) in current study) and could explain the trend of this type of cues to predict more subsequent craving. But neither substance- or person-specific cues were significant predictors of craving intensity in the current study. In this sample the association between cues and craving need to be confirmed with a higher sample size.

An important finding concerns the association between craving intensity and use of substances at the same assessment as well as over a subsequent 4-hour period. These results are consistent with previous studies revealing an association between craving and use of various types of substances in experimental (Bottlender and Soyka 2004, al'Absi, Hatsukami et al. 2005, Sinha, Garcia et al. 2006), observational (Flannery, Poole et al. 2003, Heinz, Epstein et al. 2006, Allen, Bade et al. 2008) and EMA studies (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Serre, Fatseas et al. 2018, Remmerswaal, Jongerling et al. 2019). This prospective link was lost when analyses were controlled for age, gender and the status of the substance use at T0. This result could be due to small size of the sample induced poor statistical power when model was adjusted on several variables or synergistic association of craving and substance use and will need to be replicated with a higher sample size.

In contrast to our previous study among substance users in treatment, the current analyses highlight a bidirectional association between craving and substance use. In this study substance use itself was a strong predictor of later craving, and this association remained significant when the model controlled for craving intensity at T0. The observed prospective associations are uninfluenced by the potentially synergistic association of craving and substance use, and therefore it appears that in substance users not attempting to abstain, current use aggravates the intensity of craving. The effect of substance use itself on subsequent craving showed mixed results in the literature. Some studies reported an increase of craving immediately after use, and others reported a decrease of craving after use (Serre, Fatseas et al. 2015). Thus, when people with addiction attempt to stop, substance use decreases but not craving because it persists despite prolonged periods of abstinence and is influenced by cues exposure, making craving the driving force behind use and the main risk factor for relapse (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Auriacombe, Serre et al. 2016, Auriacombe, Serre et al. 2018). When individuals use substances without attempting to quit, craving is the driving force of loss of control because even if the use is to relieve immediate

craving, it predicts a higher craving a few hours later, that forces to use a few hours later to relieve this painful experience.

Several limitations of the present study should be considered in interpreting the findings. First, the appropriate sample size for examining moderate effect sizes was estimated to 40 subjects for this study. Higher sample size should confirm tendency or clinically-significant effects, which may have been undetected by the current sample size. Craving, although considered as a characteristic of addiction, and therefore by definition observable regardless of the type of addiction, could nevertheless present variations in its expression according to the type of substances used (Serre, Fatseas et al. 2015), and the severity of the addiction (Shiyko, Burkhalter et al. 2014, Serre, Fatseas et al. 2015, Serre, Fatseas et al. 2018). Use of other substances also influences craving of main problematic substance during the same assessment (Kouri, McCarthy et al. 2004, King and Epstein 2005, Sayette, Martin et al. 2005, Serre, Fatseas et al. 2018). Our previous study among patients in treatment showed that co-use of other substances and the main problematic substance did not influence the predictive link between craving and main problematic substance use and craving of main problematic substance did not predict other substances (Serre, Fatseas et al. 2018). Substances users in this study have higher use and co-use of other substances was high, perhaps to manage the craving for the main problem substances, which could influence the relationship between craving and use of the main problem substance (frequency and quantity). It seems important in future analyses to take into account the type of substance, co-substance use and addiction severity effect on the predictive link in this severe poly-substances users not attempting to abstain treatment settings (Serre, Fatseas et al. 2018, Kervran, Serre et al. 2019).

This is a preliminary discussion of the results of an ongoing study and no final conclusion is yet possible. The study needs to be continued because some results could be due to a lack of power and are likely to become significant with more inclusions, like the association between cues and craving and craving and use adjusted on sociodemographic and use at T0. The predictive value of substance use on craving intensity seem to be reliable and may be taken into consideration as they are unlikely to change with more inclusion

Table 1. Characteristics of the sample and description of daily life variables

	%	n	Mean	SD	Min	Max
Sample characteristics (n=19)						
Gender (female)	42.1	8				
Main problematic substance use						
opiates	15.8	3				
cocaine	57.9	11				
stimulant	15.8	3				
sedative	10.5	2				
Unemployed	94.7	18				
Unstable living conditions	57,9	11				
Age			37.1	9.4	26	55
Education (years)			9.84	1.8	7	14
ASI ISR						
Medical			3.95	1.43	2	6
Employment			5.32	1.33	2	7
Alcohol			3.16	2.22	0	7
Substances ^a			5.84	1.26	4	7
Tobacco			3.26	1.15	2	7
Gambling / gaming			0.63	0.83	0	3
Eating disorders			0.47	0.70	0	2
Legal			2.53	2.27	0	7
Family / Social			3.53	2.07	1	7
Psychiatric			4.79	1.47	3	7
MINI current diagnosis						
Mood disorder	42.1	8				
Anxiety disorder	36.8	7				
ADHD	15.8	3				
Antisocial	35.3	6				
PTSD	15.8	3				
Psychotic	26.3	5				
EMA reports (observations=793)*						
Main problematic substance use (yes/no and number of use)	51.3	407	1.55	2.10	0	10
Risk practices	9.98	79				
Others substance use	77.4	613				
Co-use ^b	49.5	393				
Number of other substances use			1.37	1.08	0	7
Craving intensity			5.16	2.04	1	7
Number of substance-specific cues			7.72	5.54	0	25
Number of person-specific cues			5.13	2.97	0	13

^a included opiates, cocaine, sedatives, amphetamine, hallucinogen, inhalant; ^b Co-Use, Concomitant use of the main problematic substance and use of other substances (i.e. reported during the same assessment); *frequencies, percentages and means are based on the total number of valid electronic interviews over the assessment period.

ASI ISR: Addiction severity Index Interviewer Severity Ratings, ADHD: Attention-deficit hyperactivity Disorder, PTSD: Posttraumatic stress disorder

Figure 1: Standardized scores as a function of time in study.

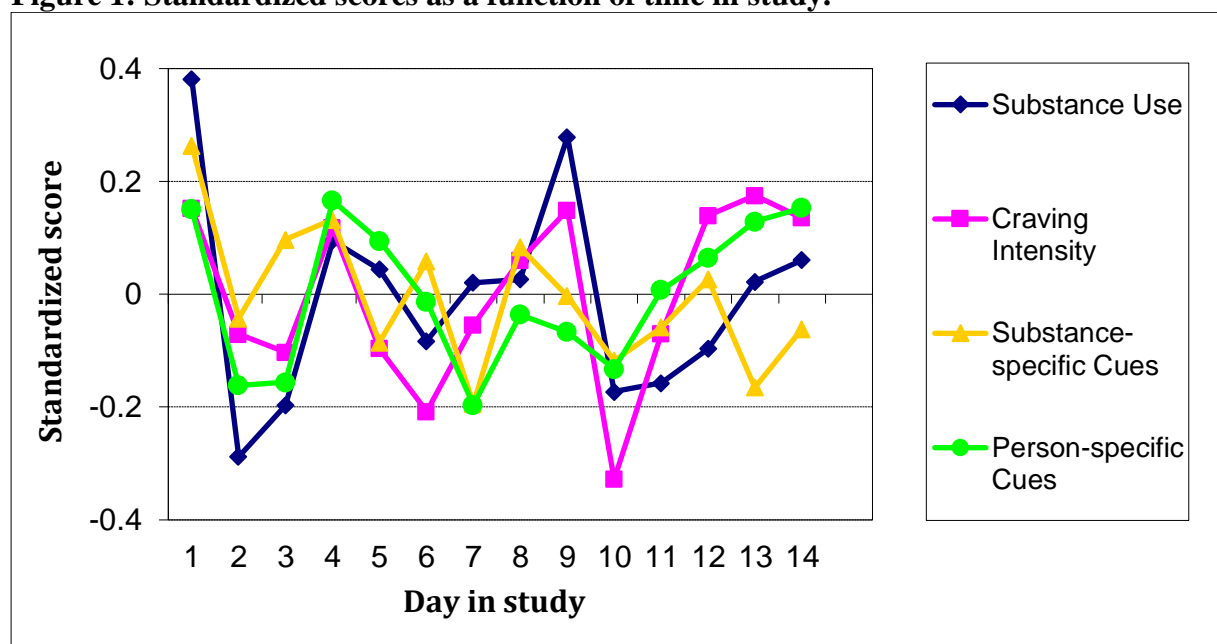


Table 2. Number and type of cues as predictors of concurrent and later craving intensity.

Predictor	Outcome	γ Coef	SE	df	T-ratio	P-value
Substance-specific Cues T0	<i>Craving T1</i>	0.036	0.018	18	1.993	0.062
Person-specific Cues T0	<i>Craving T1</i>	0.063	0.038	18	1.655	0.115

Table 3. Association of craving with main problematic substance use and infectious risk practices.

Predictor	Outcome	γ Coef	SE	df	T-ratio	p-value
Craving T0	<i>Substance use T1</i>	0.178	0.077	18	2.332	0.032
Craving T0	<i>Risk Practices T1</i>	0.205	0.14	18	1.463	0.161
Substance use T0	<i>Craving T1</i>	0.683	0.156	18	4.386	<0.001

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DISCUSSION

1 Rappel des objectifs

L'objectif principal de ce projet de thèse était de tester l'influence du contexte de soin sur l'expression de l'addiction en testant la stabilité des caractéristiques psychométriques des critères diagnostiques du trouble de l'usage du DSM-5, et la valeur prédictive du *craving* sur l'usage.

2 Mise en perspectives des résultats

2.1 Validité de la modélisation de nos populations

Un ensemble d'utilisateurs réguliers et problématiques de substances ont été recrutés dans deux contextes de soin différents choisis pour répondre à nos hypothèses.

Aucune différence de prévalence de trouble de l'usage n'a été mise en évidence selon le contexte de soin, pour les 5 substances (manuscrit 3), confirmant que les utilisateurs de substances recrutés dans un contexte de HR, sont autant malades que ceux en contexte de traitement. Ces résultats sont en accord avec les prévalences d'addiction rapportées dans des études antérieures en population de HR (Brienza, Stein et al. 2000, Ross, Teesson et al. 2002, Kidorf, Disney et al. 2004, Kidorf, Disney et al. 2005, Disney, Kidorf et al. 2006, Hides, Lubman et al. 2007, Gibbie, Hides et al. 2011). L'étude en vie quotidienne menée grâce à la méthode EMA, confirme que le contexte de HR n'influence pas l'usage de substance, à l'inverse du contexte de traitement (Fatseas, Serre et al. 2015). Au cours des 14 jours de l'étude EMA aucune diminution significative de l'usage et du *craving* n'a été observée parmi nos sujets en contexte de HR (manuscrit 6). La modélisation de sujets ayant un usage problématique activement engagés dans l'usage, et non pas dans une démarche de traitement orienté vers la réduction et/ou l'abstinence est donc valide.

En accord avec des études précédentes (Ross, Teesson et al. 2002, Moracchini, Frauger et al. 2012), les utilisateurs de programmes de HR sont plus précaires, plus jeunes et plus nombreux à avoir une poly-addiction que les utilisateurs en contexte de traitement (manuscrit 4). Parmi les utilisateurs actuels de chaque substance, les utilisateurs de programme de HR sont significativement moins nombreux à rapporter leur usage de substance comme un problème principal, alors même qu'ils consomment plus que les utilisateurs en contexte de traitement. Cela pourrait être dû à un défaut d'*insight* (conscience du trouble) (Markova and Berrios 1992), ou parce que d'autres problèmes éclipsent ceux liés à l'usage de substances (p. ex. les conditions socio-économiques), ou parce que l'usage était motivé par l'automédication d'autres troubles psychiatriques (Turner,

Mota et al. 2018). Dans certains contextes et conditions de vie, certaines personnes font usage de substances par habitude. Le fait que les substances soient facilement disponibles, que la vie de l'utilisateur tourne autour des substances (usage, deal) et qu'il ait du *craving* pour ces substances, peut ne pas être perçu comme problématique (Pickard and Ahmed 2016).

Ces résultats appuient la validité de nos modèles et le fait que nous n'avons pas étudié les mêmes usagers de substances recrutés dans des lieux différents, mais bien des sujets différents dans des contextes de soin et d'usage différents.

2.2 La stabilité des critères diagnostiques et la place du critère « *craving* »

Conformément aux études antérieures, l'unidimensionnalité du trouble de l'usage a été confirmée pour l'alcool, les opiacés, la cocaïne et le cannabis, ce qui appuie davantage le changement du DSM-5 (Hasin, Fenton et al. 2012, Hasin, O'Brien et al. 2013). Les analyses d'IRT des critères diagnostiques du trouble de l'usage DSM-5 parmi les usagers problématiques de substances, qui incluent le critère "*craving*", sont peu nombreuses, et peu d'entre elles ont exploré spécifiquement les paramètres du critère "*craving*" (Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015, Serier, Venner et al. 2019). Dans notre échantillon d'usagers de substances en demande de traitement, quelle que soit la substance, le "*craving*" était le critère le plus sélectif, car il s'ajustait mieux au modèle à un facteur que les autres critères, il était parmi les plus fréquents, et avait un pouvoir discriminatif plus marqué que les autres critères. Des résultats similaires ont été obtenus sur le pouvoir discriminatif du critère "*craving*" en population clinique et générale (Mewton, Slade et al. 2010, Keyes, Krueger et al. 2011, Shmulewitz, Keyes et al. 2011, Chung, Martin et al. 2012, Gilder, Gizer et al. 2014). Ces résultats indiquent que le critère diagnostique "*craving*" est retrouvé chez les sujets avec un trouble de l'usage de substance peu sévère, ce qui confirme son utilité potentielle en tant qu'indicateur précoce des troubles de l'usage de substances (Chung, Martin et al. 2012). En accord avec les études précédentes, les analyses de l'information totale ont montré l'absence d'augmentation significative de l'information totale lorsque le critère "*craving*" a été ajouté pour la majorité des substances, suggérant qu'il est largement redondant avec les autres critères (Cherpitel, Borges et al. 2010, Keyes, Krueger et al. 2011, Hasin, O'Brien et al. 2013). La "redondance" du critère "*craving*" peut être la manifestation du fait qu'il soit le meilleur indicateur du trait latent sous-jacent : le trouble de l'usage.

Alors qu'aucune étude n'a étudié la répartition des critères diagnostiques individuellement au sein d'usagers de substances en contexte de HR (manuscrit 2), ce travail montre que l'ensemble des critères diagnostiques étaient rapportés par les usagers de substances, quel que soit le contexte de soin. Aucun critère n'était significativement plus prévalent ou ne fonctionnait significativement différemment par rapport au trait latent sous-jacent de façon systématique pour un contexte de soin et pour chaque substance.

Parmi les critères de perte de contrôle, seul le critère "*craving*" ne présentait pas de différence de prévalence entre les deux échantillons et cela pour les cinq substances. Les critères présentant une différence significative étaient généralement plus fréquemment retrouvés chez les usagers de substances en contexte de traitement (manuscrit 4). Cependant les analyses IRT et particulièrement l'étude des différences de fonctionnement des critères (DIF), montrent que les critères "*craving*", "usage en plus grande quantité que prévu" et "temps passé à faire usage" fonctionnaient de la même façon quel que soit le contexte de soin, pour les 5 substances étudiées (manuscrit 5). Seul le critère évaluant le "désir persistant, ou les efforts infructueux, pour diminuer ou contrôler l'usage" de cannabis et de tabac, était plus fréquent chez les sujets en contexte de traitement que chez les usagers en contexte HR pour une même sévérité du trouble. Les usagers de substances dans les milieux de HR pourraient être plus intéressés à réduire les conséquences négatives, qu'à contrôler l'usage du cannabis ou du tabac, si leur usage n'est pas perçu comme un problème (Pickard and Ahmed 2016).

Les résultats concernant les critères de conséquences de la perte de contrôle sont plus complexes. La comparaison des prévalences des critères pris individuellement entre les deux populations montre qu'il existe une variabilité selon les critères et selon les substances. Parmi les critères d'adaptation pharmacologique, seul le critère de "sevrage" avait une prévalence significativement différente (cocaïne et cannabis) et un fonctionnement différent (cocaïne) selon le contexte de soin. Le sevrage est un critère qui reflète un usage excessif et répété à la fois en tant que processus physiologique et psychologique, et qui est établi sur des symptômes particulier à chaque substance (Hasin, Hatzenbuehler et al. 2006, American Psychiatric Association 2013). Les symptômes de sevrages sont directement liés à la quantité et la fréquence de l'usage, et sont donc dépendants de nombreuses variables susceptibles de modifier l'usage comme le contexte de soin et d'usage, mais aussi la disponibilité de la substance. Les critères évaluant l'usage à risque et l'altération du fonctionnement social sont dépendants du contexte d'usage, de soin, des caractéristiques socio-économiques et sociodémographiques de chaque individu (Keyes and Hasin 2008, Caetano 2011, Martin, Langenbucher et al. 2014). Ainsi, les différences de prévalences et les fonctionnements différentiels des critères de

conséquence de l'usage selon le contexte de soin ne sont pas surprenants au vu des nombreuses différences entre nos populations.

Malgré ces différences de fonctionnement selon le contexte de soin, les diagnostics du trouble de l'usage en général ne devraient pas être affectés. Les analyses de fonctionnement différentiel du "Test" indiquent que le nombre de critères approuvés ne devrait pas différer par un ou plusieurs critères pour le même degré de sévérité du trait latent entre les deux contextes de soin (manuscrit 5). Ce n'était pas le cas pour les critères opiacés et cannabis, qui différaient d'au moins un critère selon le contexte de soin, pouvant impacter le diagnostic. Cette différence n'était pas liée à un fonctionnement différentiel spécifique de critères pour les opiacés, mais sûrement à une différence de prévalence générale des critères de conséquences de l'usage (manuscrit 4). En ce qui concerne le cannabis, le fonctionnement différentiel d'un critère semble être la cause de la différence du fonctionnement du diagnostic du trouble de l'usage. Ce critère pour le cannabis pourrait produire un biais de mesure et devrait être soit supprimé, soit modélisé comme un élément distinct lorsqu'il est administré à des groupes différents. Il sera utile de comprendre les causes exactes de ce DIF dans les études futures.

Pour le tabac, certains indices d'ajustement ont confirmé l'unidimensionnalité, d'autres non. Il est intéressant de noter que la saturation des critères de conséquences de l'usage suggérait leurs limites comme indicateurs du trouble. Lors du passage du DSM-IV au DSM-5, les changements apportés au trouble de l'usage de tabac étaient bien plus importants que pour les autres substances, car ce n'est pas un seul critère qui a été ajouté (" *craving* "), mais 4 critères avec ceux de l'abus du DSM-IV. L'applicabilité des critères d'abus du DSM-IV au tabac a été controversée (Hughes, Helzer et al. 2006, Hasin, O'Brien et al. 2013). Les analyses de DIF en fonction du contexte de soin ont mis en évidence des différences de fonctionnement pour 4 critères diagnostiques tabac dont 2 critères d'abus du DSM-IV. Ces résultats ne sont pas en accord avec d'autres études en population générale et cliniques dans d'autres pays, dans lesquelles les 11 critères s'ajustaient bien au facteur à une dimension (Shmulewitz, Keyes et al. 2011, Chung, Martin et al. 2012, Shmulewitz, Greene et al. 2015). Des études supplémentaires dans des échantillons plus larges et de différents pays sont nécessaires pour éclairer l'applicabilité des 11 critères DSM-5 au tabac.

2.3 La valeur prédictive du *craving* sur l'usage

Selon la revue de la littérature il semble que parmi les participants aux programmes de HR, plus de la moitié des usagers de substances rapporte du *craving* modéré à sévère (Gu, Wang

et al. 2009). Il est intéressant de noter que les usagers de substances dans des environnements propices à l'usage, comme les programmes de HR, étaient tout autant à rapporter le critère diagnostique "*craving*" dans les 12 derniers mois et rapportaient une intensité de *craving* égale aux usagers de substances en contexte de soin sur les 30 derniers jours. L'expérimentation du *craving* ne semble donc pas être influencée par le contexte de traitement orienté vers l'abstinence. Cependant la fréquence des épisodes de *craving* paraît être dépendante du contexte de soin et de l'usage (manuscrit 4). Dans l'étude en vie quotidienne mesurant l'intensité du *craving* toutes les 4 heures environ, l'intensité moyenne sur les 14 jours d'EMA était plus élevée que pour des sujets en contexte de traitement (Fatseas, Serre et al. 2015). Cela peut s'expliquer par l'environnement de traitement orienté vers le management du *craving* par des actions éducatives, psychothérapeutiques et pharmacologiques contribuant à l'intensité moyenne plus faible et la diminution de l'intensité du *craving* au cours de l'étude.

Le modèle « *Cues-Craving-Use* » de l'addiction selon le contexte de soin semble présenter des variations. Cependant dans les deux contextes, le *craving* est au centre du comportement d'usage problématique de substances.

Une constatation importante de l'étude en vie quotidienne concerne l'association prospective entre l'intensité du *craving* et l'usage de substance. Ces résultats vont dans le sens des études antérieures en vie quotidienne révélant la valeur prédictive du *craving* sur l'usage de divers types de substances (Fatseas, Serre et al. 2015, Remmerswaal, Jongerling et al. 2019). Toutefois, contrairement à l'étude chez les usagers de substances en contexte de traitement, les analyses actuelles mettent en lumière la nature bidirectionnelle de l'association entre le *craving* et l'usage de substance. L'augmentation de l'usage de substance était un fort prédicteur de l'augmentation de l'intensité du *craving* quelques heures plus tard. Cependant, cet effet a donné des résultats plus mitigés dans la littérature. Certaines études ont fait état d'une augmentation du *craving* immédiatement après l'usage et, au contraire, d'autres ont fait état d'une diminution après l'usage (Serre, Fatseas et al. 2015). Les études précédentes montrent que les personnes ayant une addiction en tentative d'arrêt, diminuent leur usage de substance, mais le *craving* qui persiste et varie en intensité sous l'influence de l'exposition aux *cues* est un fort prédicteur de l'usage et le principal facteur de risque d'usage (Fatseas, Serre et al. 2015, Auriacombe, Serre et al. 2016). Lorsque les personnes consomment activement, le *craving* semble être la force motrice de la perte de contrôle. Si l'usage vise à soulager le *craving* immédiat (George and Koob 2013), il semble prédire une augmentation de l'intensité du *craving* contraignant à faire usage quelques heures plus tard pour soulager cette expérience douloureuse. Ces résultats appuient le rôle central du *craving* dans la perte de contrôle quel que soit le contexte d'usage et

de soin, apportant une justification supplémentaire à son rôle pronostique de la perte de contrôle.

3 Limites

Population

Les modélisations de nos populations cliniques présentent quelques limites. Il est à noter que les usagers de substances en demande de traitement ne sont pas en demande d'aide pour toutes les substances consommées de façon régulière au moment de leur arrivée en traitement. La plupart arrivent en traitement pour un objet d'addiction principal. Cependant ils sont inscrits dans une démarche de traitement dans un centre où l'addiction est considérée comme un trouble ayant le même fonctionnement, quel que soit l'objet.

Inversement les usagers fréquentant les programmes de HR, peuvent exprimer un désir d'aide supplémentaire pour leur usage problématique, mais il n'en reste pas moins qu'en venant aux programmes de HR ils sont dans une démarche d'usage actif de substance. Les usagers de substances ayant un trouble de l'usage ne sont pas des individus statiques dans leurs comportements, leurs attentes et besoins, ils peuvent passer d'un contexte de soin à l'autre. C'est pourquoi nous avons décidé de modéliser nos échantillons en tenant compte de critères stables comme l'usage régulier sur les 12 derniers mois, permettant d'observer des critères diagnostiques évalués sur 12 mois, et les lieux de recrutement qui ont des objectifs de soins (perte de contrôle vs dommages liés à l'usage) et des contraintes (favorisant la réduction de l'usage vs favorable à l'usage) très différents.

Il serait intéressant de reproduire ces analyses en comparant des usagers réguliers en demande de traitement pour une substance spécifique, à des usagers ne déclarant aucune demande de traitement pour cette même substance. Cela permettrait d'évaluer l'impact de la demande de traitement sur le comportement psychométrique des critères diagnostiques.

Données auto-rapportées

Le caractère auto-rapporté des données recueillies était susceptible d'induire des biais de désirabilité sociale, et conduire les usagers de substances à cacher certaines consommations. Cependant, plusieurs précautions ont été prises afin d'éviter cela. Les sujets étaient informés du caractère confidentiel de l'étude. Ils étaient assurés que leurs réponses ne seraient pas communiquées aux professionnels des structures et qu'elles n'influenceraient pas leur accompagnement dans les centres de soins. De plus, l'usage auto-déclaré de substance tend à être exact en l'absence de sanctions (Magura, Goldsmith et al. 1987). Une étude réalisée par notre équipe auprès de sujets de la cohorte ADDICTAQUI, a démontré une bonne validité des

données auto-rapportées d'usage de substances en comparaison aux résultats de dosages urinaires biologiques (Denis, Fatseas et al. 2012). Une autre limite concernait l'utilisation de programmes prédéfinis dans les tablettes tactiles pour l'étude EMA, qui ne permettait pas d'explicitier ou de reformuler les questions en cas de mauvaise compréhension. Cependant, afin de prévenir ces difficultés, les sujets étaient préalablement familiarisés avec l'ensemble des questions lors d'un entretien d'entraînement en présence d'un évaluateur formé.

L'évaluation du craving

L'évaluation du *craving* comme critère diagnostique et comme phénomène dynamique (EMA) était réalisée à l'aide d'un item unique ne permettant pas de prendre en compte l'aspect multidimensionnel du *craving*. La fiabilité d'une telle mesure peut être discutée (Sayette, Shiffman et al. 2000). Cependant, le choix d'un item-unique pour le critère diagnostique permet d'être en conformité avec les autres critères du MINI explorant chacun des critères diagnostiques grâce à une question unique (Sayette, Shiffman et al. 2000, Tiffany and Wray 2012, Sayette 2016). Le choix de cet outil unique pour l'étude en vie quotidienne se justifiait par le besoin d'une mesure simple et rapide, applicable à toutes les substances, et permettant d'être intégrée à des questionnaires de courte durée et répétés dans le temps (Sayette 2016). De plus, une bonne corrélation entre échelle unique et échelles multidimensionnelles du *craving* a été montrée (Vorspan et al., 2012). Néanmoins il y a toujours une limite à la comparaison de nos résultats avec ceux des études précédentes de par le fait que le critère peut être formulé et recueilli différemment (auto-questionnaire, hétéro-questionnaire, niveau de compréhension du sujet). L'évaluation du *craving* en vie quotidienne était réalisée à l'aide d'une échelle visuelle numérique. Ce type d'échelle a montré une bonne sensibilité aux fluctuations rapides d'états psychologiques (McCormack, Horne et al. 1988). Le terme *craving* est peu utilisé dans le langage courant francophone. Afin d'éviter des difficultés de compréhension, nous l'avons traduit dans le libellé de la question par "envie de consommer la substance". Dans ce projet de thèse, nos mesures du *craving* répondent aux exigences minimales, qui sont que les items utilisés couvrent un large éventail de la sévérité du *craving*, ont un contenu qui reflète le concept de besoin en tant qu'état de désir/envie et incluent à la fois des échelles dichotomiques (oui/non) et continues d'évaluation (numérique) (Tiffany and Wray 2012).

Stratégie d'analyse

La taille de l'échantillon du groupe recruté en contexte de HR était plus faible pour certaines substances, ce qui a pu avoir une incidence sur les résultats. Un échantillon plus large donnerait des estimations plus précises, des erreurs plus faibles et une plus grande capacité à

détecter les différences pour les analyses de DIF. Le modèle MIMIC est la méthode recommandée pour les petits échantillons comme dans le groupe HR, mais cette méthode ne permet pas d'évaluer les DIF non uniformes (Woods, Oltmanns et al. 2009). Il serait nécessaire de confirmer ces résultats avec un plus grand échantillon de sujets HR et de tester le DIF non uniforme pour vérifier si le pouvoir de discrimination élevé du critère "*craving*" diffère selon le contexte de soin.

Des études montraient des différences de *craving* en fonction de la substance à l'origine de la prise en charge et les autres substances consommées (Carter and Tiffany 1999, Kouri, McCarthy et al. 2004, King and Epstein 2005, Sayette, Martin et al. 2005, Serre, Fatseas et al. 2018). D'autres variables liées à l'usage de substance peuvent également influencer l'intensité du *craving*, comme la sévérité de l'addiction ou de l'usage (Shiffman, Hickcox et al. 1997, Shiffman and Paty 2006, Buckner, Crosby et al. 2012, Shiyko, Burkhalter et al. 2014, Serre, Fatseas et al. 2015). Il faut donc faire attention à l'interprétation des résultats préliminaires de l'étude en vie quotidienne sur le lien *craving*-usage, car ceux-ci ne tiennent pas compte de la substance posant le problème principal ni de l'usage d'autres substances, très nombreux dans cette population en contexte de HR. Il est nécessaire d'inclure suffisamment de sujets par groupe de substances pour pouvoir vérifier ces résultats et contrôler sur l'usage d'autres substances. Cependant, selon l'étude (Fatseas, Serre et al. 2015) établissant le modèle « *Cues-Craving-Use* » (Auriacombe, Serre et al. 2018) celui-ci était retrouvé, quelle que soit la substance.

4 Conclusion

Nous avons confirmé, dans un échantillon d'adultes ayant un usage problématique d'au moins une substance et recrutés dans des contextes de soin variés que les 11 critères diagnostiques du trouble de l'usage DSM-5 avaient une validité dimensionnelle et structurelle. Ces résultats, précédemment rapportés dans des échantillons cliniques américains, le sont pour la première fois dans un échantillon d'usagers de France. Nos résultats montrent que les critères diagnostiques de perte de contrôle sont plus stables selon le contexte de soin, que les critères diagnostiques périphériques évaluant les conséquences négatives de l'usage. Par ailleurs, dans le débat sur l'ajout du *craving* comme critère diagnostique pour l'amélioration du diagnostic du trouble de l'usage de substance, les résultats soulignent que le critère "*craving*" est le critère le plus sélectif en raison de sa fréquence élevée et de ses caractéristiques psychométriques, comparativement aux autres critères. Ses caractéristiques spécifiques sont stables selon le contexte d'usage et de soin et quel que soit le type de substance, faisant de lui un critère important de la dimension "perte de contrôle" du diagnostic du trouble de l'usage de substance. Du point de vue dimensionnel, la méthode EMA suggère que le *craving* est le moteur de l'expression comportementale de la perte de contrôle par son lien avec l'usage actif,

indépendamment des tentatives d'arrêt. Ces résultats appuient la place centrale et intrinsèque du *craving* dans l'usage compulsif de substance, expression de la perte de contrôle, indépendamment du contexte.

5 Perspectives générales

Il est important de distinguer les caractéristiques périphériques des caractéristiques "fondamentales" ou "centrales" du trouble (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018). Les caractéristiques centrales peuvent être définies comme les symptômes et les constructions qui révèlent directement le dysfonctionnement interne sous-jacent de la pathologie, comme la perte de contrôle pour le trouble de l'usage (Martin, Langenbucher et al. 2014). Les caractéristiques périphériques n'indexent pas directement ces dysfonctionnements internes (perte de contrôle), mais ses conséquences (Martin, Langenbucher et al. 2014). Les conséquences des troubles (perte de contrôle de l'usage) ont longtemps été utilisées pour caractériser et diagnostiquer les troubles de l'usage et les troubles psychiatriques en général du fait du débat ou de l'absence de consensus sur leurs étiologies (American Psychiatric Association 1952, American Psychiatric Association 1968, American Psychiatric Association 2013). De toute évidence, l'usage et les troubles de l'usage de substance sont associés à de multiples conséquences psychologiques, interpersonnelles, sociales, éducatives, professionnelles, juridiques et sanitaires négatives. Néanmoins, l'utilisation des conséquences pour définir et diagnostiquer le trouble de l'usage pose un certain nombre de problèmes conceptuels et de mesure, car ils sont liés au contexte, déterminés de façon multiple, parfois pas causés ou exacerbés par l'usage de substances et peuvent parfois être appliqués à de multiples critères diagnostiques. Ces problèmes illustrent pourquoi les conséquences n'ont qu'une sensibilité et une spécificité modestes dans leurs associations avec l'usage excessif et avec d'autres critères diagnostiques (Martin, Langenbucher et al. 2014). Ce travail de thèse remet en question la stabilité des critères de conséquences de l'usage, car certains présentent des caractéristiques psychométriques moins performantes que les critères de perte de contrôle et leur stabilité inter-échantillon était faible. C'est pourquoi nous suggérons qu'elles devraient être considérées comme des caractéristiques périphériques plutôt que centrales des troubles de l'usage, bien qu'elles soient toujours préoccupantes et causes de souffrances (Martin, Langenbucher et al. 2014, Pickard and Ahmed 2016, Auriacombe, Serre et al. 2018). Il est nécessaire de continuer à tester leurs caractéristiques psychométriques et leur stabilité dans des échantillons plus larges avec des contextes d'usage et de soins plus variés. En ce qui concerne les critères d'adaptation pharmacologique, ils sont connus pour être très dépendants de la quantité et de la nature de la substance, et peuvent être observés sans trouble de l'usage (O'Brien 2011, O'Brien 2017). Cependant le critère de sevrage montre des caractéristiques

psychométriques intéressantes, mais pas de façon systématique entre les substances (Wu, Swartz et al. 2013), limitant son intérêt comme marqueur potentiel de l'addiction.

Plusieurs études suggèrent que le trouble de l'usage de substance doit être diagnostiqué en utilisant la dimension centrale de la maladie qui est la perte de contrôle (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018). Quelle que soit la substance, les critères diagnostiques évaluant la perte de contrôle de l'usage présentaient des caractéristiques psychométriques particulièrement intéressantes et de façon stable indépendamment du contexte de soin, faisant d'eux les meilleurs critères diagnostiques pour le trouble de l'usage.

Des études expriment la nécessité de restreindre le nombre de critères afin de faciliter l'utilisation des outils diagnostiques en clinique (Stevens, Steinley et al. 2019). Cependant il semble important de déterminer quels sont les critères les plus pertinents et les plus spécifiques du trouble pour trouver la formulation optimale permettant de diagnostiquer efficacement et précocement les troubles de l'usage.

De nombreuses autres études suggèrent que le *craving* et les autres critères de la perte de contrôle sont redondants, concluant que le *craving* n'était pas un critère intéressant à ajouter dans le diagnostic, bien que reconnaissant son intérêt comme indicateur clinique (Cherpitel, Borges et al. 2010, Hasin, O'Brien et al. 2013). En tant que critère diagnostique, le *craving* semble être le critère le plus proximal du trouble de l'usage, comparé aux autres critères dans nos analyses. Ces qualités psychométriques montrent son intérêt potentiel comme indicateur précoce du trouble de l'usage. Si le critère "*craving*" est redondant, nous soutenons qu'il devrait être maintenu, mais que certains autres critères pourraient être abandonnés. Il est nécessaire de vérifier la spécificité du critère *craving* pour l'ensemble des substances incluses dans les troubles de l'usage de substances du DSM-5 (hallucinogène, inhalant, sédatif, amphétamines). Il reste à savoir si la présence du phénomène de *craving* pourrait être suffisante pour diagnostiquer la dimension de perte de contrôle des troubles de l'usage, pour l'amélioration du diagnostic (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018).

Nos résultats préliminaires, en accord avec les études précédentes, confirment le rôle central du phénomène de *craving* dans l'addiction, par son rôle dans l'expression comportementale de la perte de contrôle. Ces résultats appuient l'intérêt de l'étude de ce phénomène comme facteur pronostique de l'usage et de la rechute et comme potentiel facteur étiologique de l'addiction. Il serait intéressant de déterminer si une mesure des fluctuations du *craving* ne serait pas le meilleur outil diagnostique et pronostique de l'addiction. L'utilisation

de la méthode EMA, permettrait, dans la vie quotidienne de chaque patient d'évaluer la fréquence et les variations d'intensité de son *craving* ainsi que l'importance de son lien avec l'usage. Une telle évaluation via une application mobile permettrait de déterminer si l'utilisateur de substances à un usage excessif en réponse à du *craving*, traduisant l'expression d'une addiction.

Ces résultats pourraient faire du *craving* un marqueur spécifique et précoce de l'addiction facilement détectable et utilisable en clinique, quel que soit le contexte de soin, et en conséquence, la cible privilégiée des interventions thérapeutiques (Auriacombe, Serre et al. 2016, Auriacombe, Serre et al. 2018)..

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