INSTITUTO DE PSIQUIATRIA - IPUB

Centro de Ciências da Saúde - CCS

Universidade Federal do Rio de Janeiro

Marcelo Piquet Carneiro Pessôa dos Santos

Hábito, Recompensa e Medo nos Transtornos Relacionados ao Uso de Álcool

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Dissertação de Mestrado submetida ao Corpo Docente do Programa de Pós-graduação em Psiquiatria e Saúde Mental -PROPSAM- do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Mestre em Psiquiatria.

Orientador:

Leonardo Franklin da Costa Fontenelle
Professor Adjunto de Psiquiatria do IPUB/UFRJ

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Resumo

Esta dissertação compreende três estudos que tratam dos transtornos aditivos e relacionados ao uso de substâncias. Dois estão relacionados às dependências comportamentais, conceito reconhecido como patologia pelo DSM-5, desde a inclusão do jogo patológico em 2013. O artigo principal é um estudo que aplicou uma nova escala (Habit, Reward and Fear Scale-HRFS) para medir motivações afetivas (recompensa e medo) e hábito, pela primeira vez usada em pacientes com transtorno relacionado ao uso de álcool em amostra de cinquenta e oito pacientes em tratamento ambulatorial e hospitalar. Foram aplicados também instrumentos diagnósticos e escalas para medir estresse, ansiedade, depressão, severidade do transtorno relacionado ao uso de álcool, severidade global de transtornos relacionados ao uso de substâncias, escalas de impulsividade e escalas de rotinas e comportamentos automáticos. Adicionalmente, as características psicométricas da escala HRFS foram testadas. Também estabelecemos como as motivações se relacionaram com as características clínicas e sócio demográficas nesta amostra. A hipótese dos autores foi confirmada e foi demonstrado que comportamentos habituais e automáticos relacionados ao ato de beber estão relacionados positivamente a escores de maior gravidade de sintomas em pacientes com transtornos relacionados ao uso de álcool. Foi encontrada correlação negativa entre o número de episódios de tratamento (em regime de internação) tanto para os indivíduos com predomínio de motivações de recompensa quanto para aqueles com preponderância de hábito o que não era esperado, já que os últimos apresentaram maior severidade clínica. A fim de explicar estes achados novos estudos serão necessários.

Abstract

This thesis comprises three studies encompassing substance-related and addictive disorders. Two of which are related to behavioral addictions, a concept adopted by DSM-5 since the inclusion of pathological gambling in 2013. The main article is a study with a new scale (Habit, Reward and Fear Scale-HRFS) used for the first time to measure affective motivations (reward and fear) and habit in patients with alcohol-related disorder in a sample of fifty-eight (inpatient and outpatient) treatment seeking subjects. Instruments to measure stress, anxiety and depression, severity of alcohol-related disorder, global severity of substance related disorders, impulsivity, routines and automatic behaviors were also applied. Additionally, the psychometric characteristics of the scale were tested. We also establish how these motivations relate to clinical and socio-demographic characteristics in this sample. The authors' hypothesis was confirmed and it was demonstrated that habitual and automatic behaviors in alcohol related disorders were positively correlated to scores of greater symptoms severity. There was a negative correlation between the number of treatment episodes (hospitalization) for individuals with a predominance of reward motivations and those with a preponderance of habit, which was not expected, since the latter presented greater clinical severity. Explanation for these findings requires new studies .

Sumário

Introdução

O uso de álcool no Brasil e no mundo representa um desafio à saúde pública, correspondendo à terceira causa de morte considerando as condições médicas potencialmente tratáveis. De acordo com o Levantamento Nacional sobre Uso de Drogas e Saúde (National Survey on Drug Use and Health- NSDUH), realizado nos Estados Unidos da América, 86.4% das pessoas com mais de 18 anos usaram álcool em algum momento de suas vidas; 70.1% no último ano e 56% no último mês. Considera-se que, na população acima de 18 anos, 9.8 milhões de homens e 5.3 milhões de mulheres preencham critérios para diagnóstico de transtornos relacionados ao uso de álcool, representando 12.6% da população americana. Estima-se, ainda, que 88.000 pessoas (62.000 homens e 26.000 mulheres) morrem por ano de causas relacionadas ao álcool. Os custos totais relacionados ao danos causados pelo uso de álcool atingem a cifra 249 bilhões de dólares por ano (PARK-LEE, LIPARI et al., 2012). Dados da população brasileira, de 2013, revelam prevalência de 13.7%, sendo três vezes maior entre os homens. Em 2012 as mortes por causas relacionadas ao álcool representaram 7.4% do total no país (GARCIA and FREITAS, 2015). Portanto, entender, tratar e prevenir os transtornos relacionados ao uso de álcool é de extrema importância.

A nosologia dos transtornos relacionados ao uso de substâncias vem evoluindo desde as primeiras versões dos manuais de classificação psiquiátrica. O DSM - The Diagnostic and Statistical Manual of Mental Disorders (ASSOCIATION, 2013), por exemplo, em sua primeira versão (DSM-I), em 1952, considerou que o uso de substâncias estava associado e era decorrência de alterações sociopáticas de personalidade. O DSM-II, em 1968, manteve os transtornos relacionados ao uso de substâncias na categoria dos transtornos de personalidade, adotou o termo dependência e incluiu, pela primeira vez, evidências físicas (como a abstinência) como critério diagnóstico. O DSM-III em 1980, classificou esta condição de forma independente e definiu critérios de uso, abuso e dependência. O DSM-IV manteve a divisão abuso/dependência e deu ênfase a critérios relacionados a disfunções executivas (ROBINSON & ADINOFF, 2016).

Em 2013 o DSM-5 aboliu a dicotomia uso/abuso e estabeleceu um continuum de níveis de gravidade com relação ao número de critérios e, pela primeira vez, definiu que um comportamento aditivo pode ocorrer sem estar relacionado a uma substância, tendo sido incluído

o jogo patológico no capítulo “Transtornos Aditivos e relacionados a substâncias” (PIQUET-PESSÔA, FERREIRA et al., 2014). Esta mudança abriu caminho para o aumento do número de estudos das chamadas “dependências comportamentais em sentido amplo” como jogo patológico, cleptomania, comprar compulsivo e sexo compulsivo, entre outros (GRANT, POTENZA et al. 2010). Diferentes estudos demonstraram nestas dependências comportamentais características clínicas e demográficas semelhantes àquelas presentes nos transtornos relacionados ao uso de substâncias como o desenvolvimento de tolerância, tentativas frustradas de interromper o comportamento, curso, idade de início e história natural similares, além de perseveração de resposta e alteração nos processos de tomada de decisão (LEEMAN and POTENZA, 2012; KRMPOTICH, MIKULICH-GILBERTSON et al. 2015). Além disso, há evidências de que estes comportamentos ativam o sistema de recompensa e motivacional de forma análoga às drogas de abuso (GRANT, POTENZA et al. 2010). As dependências comportamentais em sentido amplo foram objeto de dois estudos anexos que fazem parte desta dissertação: i) DSM-5 and the Decision Not to Include Sex, Shopping or Stealing as Addictions e ii) Opioid antagonists in broadly defined behavioral addictions: a narrative review (PIQUET-PESSÔA, FERREIRA, et al. 2014; PIQUET-PESSOA and FONTENELLE, 2016).

Uma das principais teorias sobre o desenvolvimento dos transtornos relacionados ao uso de substâncias sugere que o consumo de substâncias de reforço é, em suas fases iniciais, motivado pelo efeito positivo que causam. No entanto, com a progressão do uso, a habituação se soma às motivações positivas e comportamentos automáticos e eventualmente compulsivos se tornam mais frequentes (EVERITT and ROBBINS, 2005; EVERITT and ROBBINS, 2016).

Do ponto de vista neurobiológico a mudança do comportamento de “motivada por objetivo” para habitual parece ser mediada por sensibilização prolongada causada por substâncias de reforço e envolve o córtex pré-frontal medial e o núcleo estriado ventral, ambos envolvidos em circuitos de processamento de aprendizado e recompensa (BERRIDGE, 2012; KOOB and VOLKOW, 2016). Evidências em estudos com animais documentaram essa progressão (OSTLUND, MAIDMENT et al., 2010; RENTERIA, BALTZ et al., 2018) e os achados deste estudo fornecem evidências do mesmo fenômeno em humanos.

No presente estudo avaliamos motivações para o uso de álcool e sua relação com características clínicas e demográficas em 58 pacientes que estão em tratamento. A hipótese prevê que a preponderância de comportamentos habituais e automáticos estarão relacionados

com maior severidade clínica nos transtornos relacionados ao uso de álcool. O desenho do estudo incluiu pela primeira vez uma escala para medir motivações positivas, negativas e hábito em um mesmo comportamento. Também foram usados instrumentos diagnósticos, de severidade do alcoolismo, de severidade global de adicção, de impulsividade, de hábitos e rotinas e escalas para aferição de ansiedade e depressão.

O conteúdo desta dissertação começou a ser produzido em 2015 quando entrei no estágio probatório no CIPE para estudar o transtorno obsessivo compulsivo e sua relação com comportamentos aditivos, compulsivos e aqueles relacionados à impulsividade, sob a supervisão do Professor Leonardo Fontenelle. Os dois primeiros artigos foram produzidos e permitiram a entrada no Mestrado, onde pude desenvolver o trabalho experimental que deu origem ao artigo principal desta dissertação, tendo sido submetido e aprovado pelo Comitê de Ética em Pesquisa do IPUB-UFRJ. Os dados foram obtidos no período de junho a dezembro de 2017. No momento o artigo intitulado “Hábito, Recompensa e Medo nos Transtornos Relacionados ao Uso de Álcool” está com os revisores da European Addiction Research.

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Habit, reward, and fear in alcohol use disorder

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Running title: Habit and reward in AUD

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ABSTRACT

BACKGROUND: We assessed self-reported drives for alcohol use and their impact on clinical features of alcohol abuse patients. Our prediction was that, in contrast to "affectively" (reward or fear) driven drinking, "habitual" drinking would be associated with worse clinical features in relation to alcohol use and higher occurrence of associated psychiatric symptoms.

METHODS: Fifty-eight DSM-IV alcohol abuse patients were assessed with a comprehensive battery of reward- and fear-based behavioural tendencies. In addition, an 18-item self-report instrument (the Habit, Reward and Fear Scale, HRFS) was employed to quantify affective (fear or reward) and non-affective (habitual) motivations for alcohol use. To characterise clinical and demographic measures associated with habit, reward and fear, we conducted a partial least squares analysis.

RESULTS: More pronounced scores on the habit subscale of the HRFS were significantly associated with severity of alcohol dependence reflected across a range of domains and with decreased number of detoxifications across multiple settings. In contrast, reward-driven alcohol use was associated with a single domain of alcohol dependence, reward-related behavioural tendencies, and decreased number of detoxifications.

CONCLUSIONS: These results are consistent with a shift from goal-directed to habit-driven alcohol use with severity and progression of addiction, complementing preclinical work and informing biological models of addiction. Both reward-related and habit-driven alcohol use were associated with lower number of detoxifications, perhaps stemming from more benign course for the former and lack of treatment engagement for the latter. Future work should further explore the role of habit in this and other addictive disorders, and in Obsessive-Compulsive Related Disorders**.**

KEY WORDS: Classification, diagnosis, dependence, substance abuse, typology.

1. INTRODUCTION

Harmful alcohol consumption is responsible for 3.8% of all global deaths, 4.6% of global disabilities, and more than one percent of the gross national product (GNP) being lost in most developed countries [1]. In Brazil, it has been suggested that up to 80% of all admissions for substance dependence are due to alcoholism [2]. Accordingly, understanding the key motivations that drive alcohol abuse is critical. For many years, motivation to consume alcohol has been described as either driven by reward learning (positive reinforcement) or relief of distress (negative reinforcement) [3] More recently, however, there has been an increased interest in the role of habit formation across different substance and related addictions [4-6].

Outcome devaluation studies and Pavlovian-instrumental transfer paradigms suggest that alcohol use disorder (AUD) involves a progressive shift from goal-directed control over alcohol seeking and consumption to a more ingrained, automatic, and stimulus-driven behaviour largely independent of the expected outcome [7]. From a neurobiological standpoint, the relative transition from goal directed to habitual use of alcohol may be accompanied by a shift in behavioural control from ventral to dorsal striatum [8] and a progressive dysregulation of the hypothalamic pituitary adrenal axis, the sympathetic adrenal medullary system, and the sex steroid systems. [9]

Prevailing models provide a framework that explains chronicity and increased rates of relapse of AUD, with potential to improve or assist with personalization of treatments [10]. However, as the evidence supporting these models is based mostly on laboratory studies, research on human participants based in “real life” settings is crucial to fill a gap in the established evidence-base [7]. One exception is the recent study by Sebold et al. [11] who found that “decreased model-based” (or increased habitual) control predicted relapse in patients who also had high (mostly affective) expectancies about the effects of alcohol. Also, attempts to measure the motivations according to this model included the creation of the Reasons for Heavy Drinking Questionnaire, a 7-item self-report scale with one item addressing habitual drinking [12].

Thus, in the current study, we aimed to quantify the key drives for alcohol consumption in AUD patients, focusing on their motivations to reduce fear, to obtain reward, or to execute ingrained habits. Of note, our approach was multidimensional, thus allowing AUD patients to score similarly high on different domains of motivations. We also assessed how habit-, fear-, and reward-related motivations for alcohol use related to different sociodemographic and clinical factors in AUD patients. According to existing models that suggest habitual drinking to be an “end-state” of AUD [8], our main hypotheses were that the former would be associated with greater duration of illness, increased incidence and severity of dependence (particularly perceptual and psychophysical withdrawal), greater number of lifetime detoxifications and increased severity of anxiety, stress, and depression. In contrast, we hypothesized that affect-modulated drinking (i.e. alcohol consumption either to decrease fear or obtain reward) would be associated with a shorter duration of illness, lower severity of dependence, less lifetime detoxifications and decreased severity of comorbid affective symptoms.

2. METHODS

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square or Fishers' test (categorical variables)

or student's T test or Mann

HRFS total and subscores' internal consistency, convergent and divergent validities were established by means of Cronbach's alpha and Pearson's correlation. Convergent validities of HRSF subscores were tested in relation to ADS PPW and COH Automaticity (HRSF habit), BIS/BAS fun seeking and UPPS-P sensation seeking (HRSF reward) and BIS/BAS BIS and UPPS-P negative urgency (HRSF fear). Divergent validities were tested by performing correlations of HRSF subscales with scales other than those reported above.

To identify correlates of habit, reward and fear scores, we utilized the statistical technique of partial least squares (PLS), as detailed in [24]. PLS is a multivariate, iterative technique that constructs one or more latent factors (referred to as PLS components) that optimally explain variation in X and Y. The Y variable was total score on the habit, reward and fear scores and X variables were as follows: age, sex, alcohol dependence according to MINI, clinician's severity of alcohol and other drugs according to the ASI, age at first alcohol use, duration of alcohol use since first use (in years), age at first alcohol intoxication, duration of alcohol use since first intoxication (in years), number of alcohol or other drug detoxifications at home, therapeutic communities, psychiatric hospitals, and other hospital units, ADS loss of behavioural control, obsessive-compulsive drinking style, and perceptual and psychophysical symptoms, DASS 21 stress, anxiety and depression, BIS BAS drive, fun seeking, reward and BIS, COH routine and automaticity, and UPPS-P negative urgency, positive urgency, sensation seeking, lack of premeditation and lack of perseverance.

Unlike traditional regression, PLS is ideal in situations in which variables are correlated with each other; and when the number of variables is large in comparison to the number of cases, as was the case here. Analysis was conducted using JMP Pro software Version 13.0. Any missing data points were imputed automatically by JMP using study means. The PLS model was fitted using leave-one-out cross-validation (non-linear iterative partial least squares, NIPALS algorithm), and the optimal number of latent factors was selected by minimizing the predictive residual sum of the squares (PRESS). X variables significantly contributing to the model (i.e. explaining significant variance in disease severity) were identified on the basis of 95% confidence intervals for bootstrap distribution of the standardized model coefficients not crossing zero (N = 1000 bootstraps). Variables with Variable Importance Parameter (VIP) <0.8 were excluded.

3. RESULTS

3.1 Description of the sample

The sample (n=58) was characterized by a predominance of white (79.3%) males (72.4%) with a mean age of 39.4 (SD = 13.6) years. Participants had been alcohol free for a mean of 26.6 (SD = 24.6) days. Only 27.5% were married or within a stable relationship and just 17.2% reported being economically active. Most patients (31%) described not having a religion, 27.6% declared being Catholics, and 22.4% were Protestants. On the ASI, alcohol addiction severity was 7.67 (SD = 1.70) according to the interviewer (minimum possible score=0; maximum possible score=9) and 2.48 (SD = 1.70) according to the patient (minimum possible score=0; maximum possible score=4). Up to 81% of the sample also abused other drugs; the severity of concurrent drug abuse as per the ASI was 6.91 (SD = 3.42) according to the interviewer and 2.67 (SD = 1.73) according to the patient. Age at first alcohol use was 14.53 (SD = 3.47) years and age of first alcohol intoxication was 16.19 (SD = 3.62) years. The mean number of years since the first alcohol intoxication was 22.50 (SD =

12.12). Number of previous detoxifications for alcohol ranged from 0-10 (at home), 0-3 (at therapeutic communities), 0-15 (at psychiatric hospital), and 0-2 (at general hospital).

The number of months of spontaneous remission (not resulting from treatment) varied from none to 60 months. The amount of money spent on alcohol in the last 30 days ranged from none to 8000 Brazilian *reads* (median = 300 *reads;* 1 US dollar = approximately 3.5 *reais*). In terms of psychiatric comorbidity according to the MINI, recurrent major depressive disorder was diagnosed in 84.5% of the sample; other substance abuse in 81%; other substance dependence in 79.3%; alcohol dependence in 74.1%; antisocial personality disorder, psychotic syndromes and generalized anxiety disorder in 20.7% each; dysthymia in 19%; bipolar disorder in 17.2%; panic disorder and social phobia in 10.3% each; agoraphobia in 8.6%; and OCD and bulimia nervosa in 1.7% each. Although all patients have been diagnosed with alcohol abuse, participants described cocaine (34.5%), alcohol (27.6%), more than one substance (19%), and marijuana (6.9%) use as their most significant problems.

3.2 Differences between public and private alcohol abuse patients

As expected, inpatients (recruited in a private hospital) had a previous history of being more frequently treated in psychiatric hospitals for alcohol problems (z= -2.51; p= .01); they have also been drinking for a longer time (in months) than outpatients (z=2.06; p= .04). In contrast, outpatients (recruited in a public hospital) had a greater number of overdoses (z=-3.53; p= .00004), more severe perceptual and psychophysical withdrawal (t=2.18; df=16.5; p= .04), anxiety (t=2.05; df=56; p= .04), and depression (t=2.29; df=34.2; p=0.03). In terms of HRFS, outpatients displayed greater habit (t=2.08; df=56; p=0.04) and reward-related scores (t=2.12; df=56; p= .04). Greater severity among outpatients may reflect the fact that they all come from public services in Rio de Janeiro, which show restrictions in terms of available beds for individuals with AUD.

3.3 Habit, Reward and Fear Scale (HRFS)

The Cronbach's alpha was deemed adequate (.77) for the whole HRFS and good (.81) for its Habit subscale. Removal of different items (e.g. 3, 6, 7, 10, 14 and 16) from the Habit subscale did not increase Cronbach's alpha values, thus suggesting good internal consistency. As expected, the Habit subscale of the HRFS correlated significantly with ADS PPW (r= .40; p=0.002). However, it showed no convergent validity with the COH Automaticity scores (r= .20; p=0.13). Adequate divergent validity was confirmed by the lack of correlations between Habit and BIS/BAS fun seeking (r= .16; p=0.22), UPPS-P sensation seeking (r= -.06; p=0.64), BIS/BAS BIS (r= -.13; p=0.32), and UPPS-P negative urgency (r= -.32; p=0.80).

Cronbach's alpha of the Reward subscale of the HRFS (.72) was acceptable. Removal of different items (e.g. 2, 4, 9, 12, 15 and 17) of this subscale did not increase Cronbach's alpha values, thus supporting good internal consistency of the subscale. As expected, the Reward subscale of the HRFS showed good convergent and divergent validities for correlating with the BIS/BAS fun seeking (r= .35; p=0.006) and not correlating with the ADS PPW (r= .17; p=0.19), the COH Automaticity (r= .21; p=0.11), the BIS/BAS BIS (r= -.03; p=0.81), and the UPPS-P negative urgency (r= .05; p=0.69). However, the Reward subscale of the HRFS did not correlate to a substantial degree with the UPPS-P sensation seeking (r= .25; p=0.06).

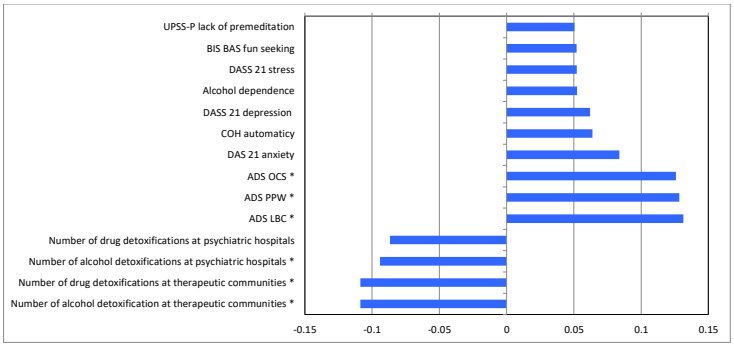
Finally, Cronbach's alpha of the Fear subscale of the HRFS (.38) was unacceptably low. In addition, poor convergent validity of the Fear subscale of the HRFS was demonstrated in the

present sample by the lack of correlations between its scores with both the BIS/BAS BIS (*r*= -.08; p=0.52) and UPPS-P negative urgency (*r*= .25; p=0.06). Further, despite lack of correlations between the Fear subscale of the HRFS with the COH Automaticity (*r*= -.008; p=0.95), the BIS/BAS fun seeking (*r*= .13; p=0.32) and the UPPS-P sensation seeking (*r*= .06; p=0.65), its divergent validity was not satisfactory, as it correlated positively with the ADS PPW (*r*= .33; p=0.01). For these reasons, PLS models with fear as Y variable of interest was not pursued.

3.4 Habit scores as Y variable of interest in PLS model

The optimal model had one latent factor, and accounted for 23.8% of variance in X variables, and 36.3% of variance in habit scores. The standardized model coefficients for each variable of interest are presented in Figure 1. Variables with positive coefficients had a positive relationship with habit scores, and vice versa. Those measures shown in bold and with an asterisk retained statistical significance by bootstrap, i.e. the 95% confidence interval of the bootstrap distribution of the model coefficient did not cross zero. Increased habitual use of alcohol in the present sample was significantly associated with greater severity of alcohol dependence in different domains (including loss of behavioural control, obsessive-compulsive drinking, and perceptual and psychophysical withdrawal) and, unexpectedly, with a decreased number of alcohol and drug detoxifications across multiple settings.

Figure 1: Standardized model coefficients for each X variable of interest in the optimal PLS model (one latent variable): Habit related scores of the HRFS as the Y variable of interest

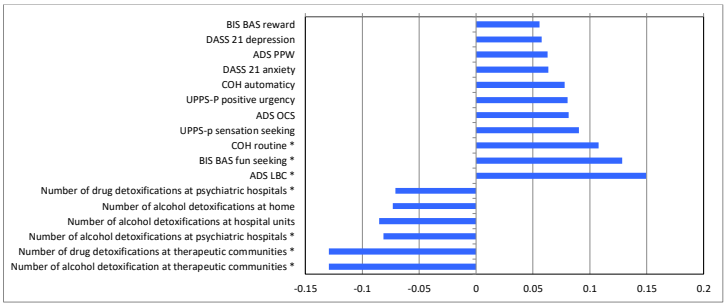


Footnote: UPPS-P= Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; BIS BAS= Behavioral Inhibition/Activation scale; DASS-21= Depression Anxiety Stress Scale; COH=Creatures of Habit, ADS=Alcohol Dependence Scale; OCS=Obsessive-Compulsive Symptoms; PPW=Perceptual and Psychophysical Withdrawal; LBC=Loss of Behavioral Control; *: statistically significant predictive variable by bootstrap.

3.5 Reward scores as Y variable of interest in PLS model

The optimal model had one latent factor, and accounted for 17.6% of variance in X variables, and 41.4% of variance in reward scores. The standardized model coefficients for each variable of interest are presented in Figure 2. Variables with positive coefficients had a positive relationship with reward scores, and vice versa. Those measures shown in bold and with an asterisk retained statistical significance by bootstrap, i.e. the 95% confidence interval of the bootstrap distribution of the model coefficient did not cross zero. Reward-related scores in the HRFS scores were associated with a single domain of alcohol dependence (namely loss of behavioural control), increased BIS BAS fun seeking, COH routine and, as expected, decreased number of alcohol and drug detoxifications.

Figure 2: Standardized model coefficients for each X variable of interest in the optimal PLS model (one latent variable): Reward related scores of the HRFS as the Y variable of interest



Footnote: UPPS-P= Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale; BIS BAS= Behavioral Inhibition/Activation scale; DASS-21= Depression Anxiety Stress Scale; COH=Creatures of Habit, ADS=Alcohol Dependence Scale; OCS=Obsessive-Compulsive Symptoms; PPW=Perceptual and Psychophysical Withdrawal; LBC=Loss of Behavioral Control; *: statistically significant predictive variable by bootstrap.

4. DISCUSSION

In this study, we used diagnostic interviews and self-report instruments to address the intensity of different motivations for alcohol use and their correlates in a clinical sample of AUD. We demonstrated that increased severity of alcohol dependence was associated with habitual use of alcohol on the HRFS, in keeping with preclinical data [8] Also in agreement with the above result, the use of alcohol for its rewarding properties on the HRFS was associated with a less generalized severity of dependence and with a range of impulsive personality features. These findings were largely consistent with our initial hypotheses. Although increased impulsivity levels, particularly UPPS-P sensation seeking [25] and BAS drive and fun seeking [26] have been reported in alcohol abuse individuals, these studies were unable to previously ascribe these psychological profiles to an specific AUD phenotype.

Despite employing a dimensional approach whose objective did not include the identification of discrete subgroups of AUD patients (the same patient could score similarly high on different motivations), our data suggest that habit- and reward-based alcohol abuse could partially map into existing subtypes of phenotypes of AUD patients, such as Babor's types A and B alcoholism, respectively [27]. For instance, habit based alcohol abuse seems to correspond to the more severe type B subgroup, which also shows a longer duration of illness and higher genetic (family history)/environmental (stress/traumatic) risk factors. In contrast, the reward-based alcohol abuse would be consistent with the less severe (type A) group of alcohol abuse, also having a shorter duration of illness and low-genetic/environmental vulnerabilities [27].

Accordingly, decreased number of detoxifications in participants using alcohol to obtain reward may also reflect a more benign course, a finding consistent with the milder subtype of alcohol abuse described above [27]. In contrast, the association between lower (rather than higher) numbers of detoxification and habitual use of alcohol contradicted our initial prediction. This novel result may be clinically important, suggesting that while habitual alcohol use is associated with more severe alcohol use pathology, such high habit scoring individuals may be less likely to 'break their habit' and seek/agree to inpatient treatment. The impact of scale scores on treatment engagement and outcomes should be explored further in future work.

We found that higher reward-driven use of alcohol on the HRFS was associated with higher 'routine' scores on the Creature of Habit (COH) scale; and that higher habit-driven use of alcohol on the HRFS tended to be associated with higher 'automaticity' scores on the COH scale (albeit the latter was not significant with bootstrap). This may reflect the nature of the COH scale items: the COH 'routine' items relate largely to comfort and the need for comfort whereas those for 'automaticity' relate more to finding oneself engaged in acts or habits without prior thought. Conceivably early alcohol use may thus be motivated by the need for comfort (i.e. reduction of anxiety) whereas later it is linked to more automatic habitual tendencies.

This study has a number of limitations, including a small and heterogeneous sample, a cross-sectional design, and the use of an instrument that still has incipient psychometric properties being evaluated (the HRFS). Further, initial predictions about fear-driven AUD could not be appropriately tested due to problems exhibited by the fear subscale of the HRFS. It is difficult to speculate on the reasons for poor convergent and divergent validities and unacceptable

intraclass correlations coefficients of this subscale, as they could reflect problems such as low numbers, items that do not address adequately the fear component of alcohol abuse or even the irrelevance of the fear construct for alcohol abuse patients (which, at least in our population, orbited around themes of reward and habit). Future studies including bigger numbers and participants with impulsive-compulsive disorders with clearer fear components, such as OCRDs, should help clarify these issues.

In conclusion, our study represents an important step towards the translation to the clinical arena of experimental human and animal research indicative of transition from goal-directed towards habitual alcohol use with more severe illness (disease progression). In the future, habit and reward subcomponents of the HRFS may be used in alcohol abuse patients to monitor evolution and select more specific treatments [10]. Use of such measures in wider contexts, such as in other substance addictions, behavioural addictions, and Obsessive-Compulsive Related Disorders, may help to advance the field and further elucidate the fit of this model to understanding different forms of psychopathology.

Appendix: HABIT, FEAR, AND REWARD SCALE (HRFS)

Please, discuss with your clinician what target behavior he/or she wants to address with this scale. Then, refer to this target behavior (e.g. wash/washing) and indicate the extent to which you agree or disagree with each statement.

TARGET BEHAVIOR: *Drink/Drinking Alcohol*

1 Strongly disagree	2 Disagree	3 Mildly disagree	4 Neither agree or disagree	5 Mildly agree	6 Agree	7 Strongly agree

1.	I _____ when I am feeling bad (with fear, guilt, disgust, concern, anxiety, shame…).	1	2	3	4	5	6	7
2.	I _____ to feel good (pleasure, joy, excitement, determination, alertness…).	1	2	3	4	5	6	7
3.	I _____ without thinking.	1	2	3	4	5	6	7
4.	I would feel frustrated if I was prevented from _____.	1	2	3	4	5	6	7
5.	I would feel fear, guilt or disgust if I couldn't _____.	1	2	3	4	5	6	7
6.	I start _____ before I realize I'm doing it.	1	2	3	4	5	6	7
7.	I _____ without having to consciously remember.	1	2	3	4	5	6	7
8.	I'm afraid of the consequences of not _____.	1	2	3	4	5	6	7
9.	_____ makes me happier.	1	2	3	4	5	6	7
10.	_____ is a part of my (daily, weekly, monthly) routine.	1	2	3	4	5	6	7
11.	_____ helps me to reduce bad feelings (fear, guilt, disgust, anxiety…).	1	2	3	4	5	6	7
12.	I like _____ and appreciate how I feel afterwards.	1	2	3	4	5	6	7
13.	I _____ because I feel I need (am compelled) to do it.	1	2	3	4	5	6	7
14.	I do not need to think about _____, it just happens.	1	2	3	4	5	6	7
15.	I appreciate _____.	1	2	3	4	5	6	7
16.	I _____ automatically.	1	2	3	4	5	6	7
17.	I give up doing things or going to places in order to _____.	1	2	3	4	5	6	7
18.	I avoid situations, places or people so I won't need to _____ even more.	1	2	3	4	5	6	7

Scoring:

Habit: 3, 6, 7, 10, 14 and 16

Reward: 2, 4, 9, 12, 15 and 17

Fear: 1, 5, 8, 11, 13 and 18

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Artigo 1 :

DSM 5 and the Decision Not to Include Sex, Shopping or Stealing as Addictions

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ADDICTIVE DISORDERS IN DSM-5 (JE GRANT, SECTION EDITOR)

DSM-5 and the Decision Not to Include Sex, Shopping or Stealing as Addictions

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Abstract For the first time substance use will not be required for the diagnosis of addiction in diagnostic classification manuals, such as *DSM* and *ICD*. The *DSM-5* has included gambling disorder, along with substance use disorders, as forms of addictions in a new chapter named "Substance-related and addictive disorders", thus reflecting evidence that gambling behaviors activate reward systems similarly to drugs of abuse. However, there is still debate on whether other less recognized forms of impulsive behaviors, such as compulsive buying (oniomania), compulsive sex, and kleptomania can be conceptualized as addictions. In this review, we critically evaluate the literature on these behaviors with a focus on socio-demographic and clinical characteristics, underlying neurobiology and treatment response, and their potential overlap with substance use disorders. We were unable to find a substantial number of studies supporting a relationship of the aforementioned reward-based conditions to substance use disorders, thus supporting the contention not to include compulsive buying, compulsive sex, and kleptomania in *DSM-5* as behavioral addictions.

Keywords Compulsive buying · Compulsive shopping · Compulsive sex · Hypersexual disorder · Kleptomania · Shoplifting · Behavioral addictions · DSM-5

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Introduction

For many years, former *DSM* versions employed the term addiction in relation to alcohol and substance use, while the pursuit of non-substance reward (e.g., excessive gambling, food and sex) was described as symptomatic of impulse control disorders or personality disorders. In *DSM-5*, for the first time since the diagnostic manuals were developed, the diagnosis of addiction will no longer be limited to substance use [1]. For instance, pathological gambling, now termed gambling disorder, has been described as a behavioral addiction under the chapter named "Substance-related and addictive disorders", reflecting evidence that gambling behaviors activate reward systems, similarly to drugs of abuse [2, 3]. In fact, there has been growing evidence that other behaviors with positive reinforcing effects may become addictive for predisposed individuals. However, the mechanisms underlying other behavioral addictions are poorly understood, in part because of the lack of animal models and brain imaging research [4••].

Although a number of reward-based conditions (such as excessive eating, sex and love, buying, exercising, gaming, tanning, tatooing, shoplifting etc.), present some phenomenological overlap with behavioral addictions, the evidence suggesting that these behaviors may develop into addictions is mostly descriptive, rather than biological or evidence-based [5]. However, the evidence suggesting that some of them (such as gambling), share features with substance use disorder is compelling. Both diagnostic groups tend to have an early age of onset and high prevalence in adolescents and young adults. The co-occurrence of behavioral addiction with substance use disorders suggests that they share dysfunction in overlapping neurocircuitry pathways involving the frontal cortex and the striatum [4••]. Also, the patterns of comorbidities in both conditions are similar, involving depressive disorders, bipolar disorders, and ADHD.

In terms of natural history, initial behavioral addictions' and substance use disorders' ego-syntonic features gradually become more habitual, automatic, compulsive and ego-dystonic. Attempts to discontinue problematic behaviors in both conditions are associated with increased levels of dysphoria. There have also been some reports of patients who switch from substance use disorders to behavioral addictions and vice-versa [6]. In addition, both may be viewed as pathological variants of normative behavior; it is sometimes difficult to set the threshold for clinical significance, which may be considered arbitrary. Finally, they often respond to the same pharmacological and psychosocial treatments, such as the 12-step based approach, cognitive behavior therapy, mu-opioids receptor antagonists, and medications that alter glutamatergic activity [7••].

While the evidence supporting the inclusion of gambling disorder as a behavioral addiction in *DSM-5* was considered sufficient, there is still debate on whether other, less recognized forms of abnormal behaviors, such as compulsive buying, compulsive sex or hypersexual disorder, and kleptomania, can be conceptualized as addictions. In this review, we critically evaluate the literature on these behaviors with a focus on socio-demographic features, clinical characteristics, treatment response and their potential overlap with substance used disorders.

Compulsive Buying

Emil Kraepelin first described compulsive buying as an impulsive insanity almost a hundred years ago [8]. Studies have shown that this condition is more prevalent in women and has its onset in the late teens and early adulthood. People suffering from compulsive buying experience repetitive, irresistible, and overpowering urges to purchase goods. In general, the goods are inexpensive and useless [9]. The diagnosis requires evidence of severe distress or interference in social, financial and occupational areas. An important difference between compulsive buyers, normal consumers, and hoarders with excessive acquisition is that the focus and excitement is not on the item bought, but on the buying process itself [10].

In compulsive buying, the overpowering urge to buy, the repetitive loss of control over spending, and the negative emotional state that emerges when not buying resemble craving, drug seeking behavior, and withdrawal symptoms in substance use disorders. Accordingly, some patients report a feeling similar to the "high" resulting from drug intoxication while performing the buying act. As in substance use disorders, positive reinforcement plays a role at the beginning of compulsive buying, while negative reinforcement is involved in the long-term maintenance of the behavior [10]. Psychiatric comorbidities in both include mood disorders, eating disorders, and other impulse control disorders. Some studies suggest that nearly 60 % of compulsive buying patients meet criteria for at least one personality disorder [11].

We found only one fMRI study showing a higher activity in the ventral striatum and a lower activation of the insula while compulsive buying patients performed purchasing related decisions [12•]. Although a role has been suggested for opiate, serotonergic, and dopaminergic systems dysfunctions in this condition, the precise alterations in these neurotransmitters are still unclear [6]. For instance, the evidence supporting the utility of serotonin reuptake inhibitors in compulsive buying is mixed, i.e., while citalopram has shown some benefit [13], escitalopram [14] and fluvoxamine did not [15, 16]. One additional concern is that the number of different buying behaviors required to qualify compulsive buying as potentially addictive, is unclear [17]. Thus, we concur with the *DSM-5* developers in that there is not enough data to classify compulsive buying as an addiction.

Hypersexual Disorder

In the 19th century, individuals who lost control over sexual behaviors were diagnosed with moral insanity, satyriasis, or nymphomania [18]. The prevalence of hypersexual disorder is estimated to be between 3 and 6 % [19]. The condition is far more common among men, begins in adolescence and early adulthood, and has a chronic course [19]. It can be hard to draw limits between hypersexual disorder and normal sexual behavior, which depends on partner's behavior, societal and moral values, and ethics and religious beliefs [20]. However, hypersexual disorder has been reported to be associated with unwanted outcomes, such as unplanned pregnancy, marital separation and divorce, and sexually transmitted diseases, including HIV infection [21, 22].

Although not formally recognized in *DSM-5* as a discrete psychiatric disorder, hypersexual disorder shares some features with substance use disorders. These include an early onset with a chronic-relapsing course that comprises pursuit of short-term reward (i.e., orgasm in hypersexual disorder or a "high" in substance use disorders), despite potential long-term negative consequences (e.g., physical or emotional harm to self or others), and frustrated attempts to inhibit or control the behavior [21]. Some have argued that, like addiction, hypersexual disorder patients may develop tolerance to increasing levels of sexual stimulation, and even withdrawal-like syndromes in the absence of sexual activities, although there are no high quality data available to prove or disprove this observation. Thus, if hypersexual disorder exists as a discrete psychiatric disorder that is independent from other existing nosological entities, phenomenological data

suggests that it could be classified as a behavioral addiction [21].

However, there is also some evident phenomenological overlap between hypersexual disorder and other groups of psychiatric disorders. For instance, it could be also classified as a non-paraphilic sexual desire disorder, as an obsessive-compulsive related disorder, or as a disruptive, impulse control, or conduct-related disorder [21]. The identification of neurobiological links between hypersexual disorder and the conditions listed under these headings could help to establish its place in the current nosological scenario. However, there seems to be no obvious answer to this question, as there is a dearth of biological studies on the topic. For instance, we are aware of only one imaging study in hypersexual disorder. In a diffusion tensor imaging (DTI), Miner et al., found affected subjects to have significantly higher superior frontal region mean diffusivity than controls, which correlated with the severity of symptoms [23••].

The lack of neurobiological studies in other areas is also noteworthy. While the same DTI study reported above found hypersexual disorder patients to show higher impulsivity scores when compared to controls in a go-non-go task [23••], another study reported cognitive rigidity, poor judgment, and deficits in emotional regulation in affected subjects [24]. There is also some evidence suggesting that hypersexual disorder may involve dysfunction in dopaminergic pathways, as hypersexuality and other uncontrolled behaviors (e.g., compulsive buying), are reported to be occasional side effects of dopamine agonists in Parkinson's disease patients [25]. Involvement of the frontal lobes, increased impulsivity, poor emotional regulation, and a relationship with disturbed dopaminergic neurotransmission suggest hypersexual disorder to be associated with behavioral addiction. However, given the scarcity of biological studies in the field, we feel that the *DSM-5* decision not to include it as a behavioral addiction was justifiable and prudent one.

Kleptomania

In 1938, Esquirol, a French psychiatrist, coined the term kleptomania as a way to describe an irresistible impulse to steal worthless objects. Although the terms shoplifting and kleptomania have been used interchangeably, the goal for the latter is generally symptom relief without financial purposes [26]. While the prevalence of kleptomania in the general population is somewhere between 0.3 and 0.6 % [2], shoplifting is far more common, affecting up to 11.3 % of the population in their lifetime [27]. Although most stolen objects are worthless and inexpensive, shoplifters are responsible for almost US $11.7 billion in retail losses per year in the USA [28]. Kleptomania affects more women than men and begins in adolescence and early adulthood [29].

Typically, once a kleptomania patient steals an item, the stolen items are hoarded, thrown away, or secretly returned. Most patients keep the condition secret until consequences become severe. In fact, patients usually present for treatment by legal mandate due to repeated shoplifting [30]. Kleptomania is associated with high rates of suicide attempts [31]. Some cases are triggered by medications (e.g., serotonin reuptake inhibitors) [32], and may emerge during specific medical conditions, such as Neuro-Behçet's disease [33]. Studies have found high lifetime rates of comorbid mood (59 to 100 %), anxiety (60 to 80 %), impulse control (20 to 46 %), and substance use disorders (23 to 50 %) [34].

Currently, kleptomania is under the chapter "Disruptive, Impulse-Control, and Conduct Disorders" in the *DSM-5* [2]. However, as the compulsive component becomes more evident, researchers have suggested that it should be best characterized either as an obsessive-compulsive related disorder, or as a behavioral addiction. While the first view is based on the presence of repetitive thoughts, irresistible urges and uncontrolled behaviors related to stealing, and on the high rate (63 %) of hoarding found among patients with kleptomania [7••]; the disorder also resembles substance use disorders on phenomenological and, at least preliminarily, on the biological level.

Like many other impulse control disorders, kleptomania is characterized by a chronic relapse pattern, with pursuit of short term reward, the sense of a "high" while committing the act, successive attempts to control or stop the behavior, and feeling of shame and guilt after the behavior. From the neurobiological standpoint, studies showing poor white matter integrity in ventral-medial-frontal regions [35•], positive response to opioid antagonists [36••], and lack of response to serotonin reuptake inhibitors [37], all suggest that kleptomania may be classified as a behavioral addiction. However, to date, neurobiological studies are too few to provide a definitive answer with regard to the nosological status of this condition.

Conclusion

Although there is a consensus on the identification of gambling disorder as a behavioral addiction, there is no agreement on whether other excessive behaviors with mixed impulsive and compulsive features (such as compulsive buying, hypersexual disorder, and kleptomania), are related to substance use disorder and should therefore be considered as behavioral addiction. In addition to neuroimaging, which has begun to unveil similarities and differences among individual behavioral addictions, and between behavioral addictions and SUD, further molecular, cognitive, and computational research will be valuable in delineating the boundaries and location of behavioral addictions in dimensions of psychopathology [4••].

Compliance with Ethics Guidelines

Conflict of Interest Marcelo Piquet-Pessôa, Gabriela M. Ferreira, Isabela A. Melca, and Leonardo F. Fontenelle, declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Artigo 2:

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REVIEW

Opioid antagonists in broadly defined behavioral addictions: a narrative review

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ABSTRACT

Introduction: Naltrexone (NTX), a mu-opioid receptor antagonist, has been approved for the treatment of alcoholism and opioid dependence. More recently, however, NTX and a related drug, nalmefene (NMF), have also shown positive results for the treatment of gambling disorders.

Areas Covered: In this study, we reviewed the trials testing the effect of opioid antagonists (OA) in gambling disorders and in other broadly defined behavioral addictions, including selected DSM-5 disruptive, impulse-control, and conduct disorders, obsessive-compulsive and related disorders, eating disorders, and other conditions not currently recognized by official classification schemes. We found six randomized controlled trials (RCTs) of OA in gambling disorder, two RCTs of OA in trichotillomania (hair pulling disorder), two RCTs of OA in binge eating disorder, and one RCT of OA for kleptomania. We also reviewed case reports on hypersexual disorder, compulsive buying and skin picking disorders.

Expert Opinion: The reviewed data supported the use of OA, namely NTX and NMF, in gambling disorder (both) and kleptomania (NTX). We did not find enough evidence to support the use of NTX or NMF in trichotillomania (hair pulling disorder), excoriation (skin-picking) disorder, compulsive buying disorder, hypersexual disorder, or binge eating disorder.

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1. Introduction

The DSM-5 has listed gambling disorder (GD) as a 'behavioral addiction', based on its phenomenological and neurobiological similarities with substance use disorders (SUDs).[1,2] For instance, different studies have shown the development of tolerance, frustrated attempts to stop the behavior and similar courses, outcomes, natural histories, and age of onset in both conditions. Also, SUD and GD subjects present dysfunctional decision-making processes,[3] impulsive action and choice [4] and response perseveration.[5] Evidence from neuroimaging studies has shown reward-related deficits in both conditions.[6–8]

In contrast, there has been dispute on whether other disorders characterized by excessive hedonic behaviors, here termed broadly defined behavioral addictions, should be classified under the same epitome of SUD and GD.[9] Like individuals with SUD and GD, individuals with other types of behavioral addictions exhibit impaired self-control, functional impairment, and persisting engagement in the behaviors despite negative consequences.[10] Though the amount of research supporting their inclusion in classification manuals is much sparse, kleptomania,[11] hypersexual disorder (HD),[12] compulsive buying,[13] and obesity/food addiction,[14] among others, have all shown several similarities with addictions.

There has been a lot of interest in the ability of the mesolimbic circuit to mediate reward, learning, and salience attribution in normality and across different addictive conditions.[8,15,16] Accordingly, the pharmacological approach to treat SUD has been to modulate reward mechanisms with medications that alter mesolimbic circuits via glutamatergic, serotonergic, dopaminergic, and opioidergic transmission.[17–19] Perhaps the drug that has been most well studied in this regard is the opioid antagonist naltrexone (NTX).[19–20]

The use of opioid antagonists to treat alcohol use disorder was based on preclinical studies showing that the amount of dopamine release and the self-administration of alcohol were diminished in animals treated with NTX.[21,22] The US FDA approved NTX for the treatment of alcohol dependence in 1994. Nalmefene (NMF) was developed in the early 1970s, and currently its use as oral formulations is approved only in Europe for the treatment of alcohol use disorders.[23,24]

Both NTX and NMF are mu-and delta-opioid receptor antagonists, with NTX also acting as a kappa-receptor antagonist, and NMF acting as a kappa-receptor partial agonist.[25] The effect of NTX (and probably NMF) on addiction is thought to stem from its ability to modulate the effects of the arcuate nucleus' opioid neurons on the ventral tegmental area/mesolimbic dopamine circuitry, [26] leading to diminished urges to engage in the addictive behaviors and longer periods of abstinence.[27]

Based on the similarities of broadly defined behavioral addictions and SUD and on the effect of NTX and NMF in alcohol use disorders, we aimed at reviewing the studies testing the effect of opioid antagonists in the treatment of the former group of conditions, including GD, kleptomania, HD

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Article highlights

- In this study, we evaluated the effect of opioid antagonists in broadly defined (including nonofficial) behavioral addictions.
- We found evidence supporting the use of opioid antagonists in GD and kleptomania.
- However, evidence for the use of opioid antagonists in other 'behavioral addictions' is still insufficient.

This box summarizes key points contained in the article.

and related disorders, compulsive buying, binge eating disorder (BED), excoriation (skin picking) disorder, and trichotillomania (TTM or hair-pulling disorder).

2. Methods

A search was conducted in PubMed and Medline combining the terms: 'behavioral addictions' OR ('compulsive buying' OR 'binge eating disorder' OR 'gambling' OR 'hypersexual*' OR 'kleptomania' OR 'trichotillomania' OR 'skin picking') AND ('opioid antagonists' OR 'naltrexone' OR 'nalmefene'). No date limit was defined for the search and all articles were in English. We were specifically interested in identifying controlled trials, open studies, cases series, or case reports. The search generated a total of 477 articles. Relevant trials, including opioid antagonists in the treatment of broadly defined behavioral addictions, were selected, including a total of 1079 subjects assigned either to NTX, NMF, or other opioid antagonists. We have created a table describing the studies addressing the effect of opioid antagonists on each condition.

3. Results

3.1. Gambling disorder

GD is characterized by persistent and maladaptive patterns of gambling behaviors. It affects between 1% and 3% of the North American adult population during their lifetime.[28,29] However, GD has been described in different cultures, thus representing a worldwide problem.[30] It is the first non-substance addiction to be officially recognized by psychiatric official nomenclature (APA, 2013). People with GD present reduced quality of life, high rates of divorce and bankruptcy, and increased frequency of suicide attempts.[31,32] Importantly, GD is also associated with high rates of general medical problems, such as hepatic and cardiac diseases.[33,34]

NTX, an FDA-approved agent for use in alcoholism and opioid dependence, is the most studied mu-opioid antagonist for the treatment of GD.[27,35,36] To date, one open-label and three double-blind placebo-controlled trials have been conducted evaluating the effect of NTX in GD (including a total of 235 patients) and two studies investigated the effect of NMF [37] in the treatment of the same condition (including a total of 440 patients).

3.1.1. Naltrexone

The first trial to evaluate the short-term effect and safety of NTX for GD was conducted by Kim and Grant in 2001. This was the first study to use a specific scale to evaluate changes in gambling symptoms during treatment (GSAS-gambling symptoms assessment scale). In this 6-week trial, 17 subjects were enrolled (seven men and 10 women). The starting dose of NTX was 25 mg/day and after 2 days the dose was increased to 50 mg/day for 7 days. Increments of 50 mg a week were done until positive response was achieved (after clinical evaluation) or the total dose reached 250 mg/day. The therapeutic effect was noted at the fourth week. The average dose was 157 mg/day. Nausea (47%), diarrhea (41%), drowsiness (38%), and insomnia (38%) were the most common side effects. All outcome measures have shown significant reductions during treatment, including gambling urge strength, frequency, and duration; gambling thought frequency and duration; subjective distress and amount of money lost. Also, clinician- and patient-rated clinical global impression (CGI) scores diminished.[37]

In 2001, Kim et al. published the first double-blind placebo-controlled study on the efficacy of NTX in GD. In this 18-week study, the mean daily dose of NTX was 188 mg. The NTX group showed significant improvement in all measures. More specifically, 55%, 20%, and 10% of patients in the NTX group were considered very much improved, much improved, and minimally improved, respectively, In contrast, 12%, 12%, and 40% of patients in the placebo arm were considered responders according to the same criteria (based on the using the Gambling Symptom Assessment Scale). Nausea (45%), dry mouth (40%), and vivid dreams (40%) were the most common adverse effects seen in the NTX group. The subjects who had higher levels of urges at baseline visit reported better response to NTX than placebo, compared to those with low and moderate urges at baseline evaluation.[35] A similar phenomenon has been reported in alcohol use disorders.[38,39]

In 2005, Dannon et al. published an open-label study evaluating the effect of sustained-release bupropion versus NTX in the treatment of GD. The inclusion criteria comprised a South Oaks Gambling Screen (SOGS) score of at least 5, DSM-IV criteria for GD, and age between 18 and 65 years. Thirty-six subjects were enrolled and randomized to bupropion slow-release tablets (n = 17, 150–450 mg) or NTX (n = 19, 25–100 mg). After three weeks, 50 mg of NTX was added (to a total of 150 mg) to 6 of 19 patients who did not respond or only partially responded to NTX. There were 12 completers in the bupropion group and 13 completers in the NTX group. A full response, defined as a 2-week period of absence of gambling behavior, was obtained by 12 out of 17 patients in the bupropion group and 13 out of 19 patients in the NTX group, thus not differing between arms. As this study did not include a placebo group, its results could be due to a placebo effect. [40]

In 2008, Grant et al. published another 18-week, double-blind, placebo-controlled study of NTX in the treatment of pathological gambling urges. Patients were randomly assigned to placebo and NTX (50, 100, and 150 mg/day). The gambling symptoms were assessed using the pathological gambling adaptation of Yale-Brown Obsessive Compulsive Scale (PG-YBOCS) as the primary outcome measure. The

number of subjects who completed the study was 36 (62.1%) in the NTX group and 13 (68.4%) in the placebo group. NTX was well tolerated and no statistical difference was found between groups regarding adverse effects. However, significant improvement for the NTX group was found, i.e. while 23 subjects (39.7%) were able to stop gambling for 1 month, only two (10.5%) from the placebo group were able to do so.[36]

In 2009, a study performed by Toneatto et al. aimed at establishing the efficacy of NTX for alcohol abusers with GD. Remarkably, all subjects received seven sessions of cognitive behavior therapy during this study. After randomization, 52 subjects were assigned to take NTX or placebo. The majority of the sample (80% of placebo and 63% of NTX treated subjects) presented no adverse effects. The most common adverse effect was nausea or vomiting (14.8% for NTX and 4% for placebo). The experimental hypothesis, i.e. that NTX would be superior to placebo in reducing alcohol and gambling behaviors in a comorbid sample, was not supported. The authors reported that the inability of this trial to identify differences between groups could be ascribed to the fact that cognitive behavioral therapy was provided for all subjects, that the sample size was small, and that the attrition rates were high.[41]

In 2010, an open pilot study by Lahti et al. tested the effect of 50 mg of NTX on an 'as needed basis' (i.e. when craving to gamble) in 39 GD patients. The DSM IV criteria and the SOGS were used to select subjects. The authors found a significant decrease in reported 'obsessive compulsive' gambling symptoms measured by Yale Brown Obsessive Compulsive Scale modified for pathological gambling (YBOCS-PG).[42] However, in 2016, the same group tested the effect of NTX on an 'as needed basis' in a randomized, placebo-controlled study. It is important to mention that this was the first study to evaluate whether a polymorphism of the opioid receptor mu 1 (OPRM1 A118G) gene was implicated in moderating treatment response in NTX therapy for GD. The inclusion criteria comprised a SOGS Revised (SOGS-R) score of 5 or more, age of at least 18 years, ability to speak Finnish, and DSM-IV criteria for GD.

After randomization, Kovanen et al. gave GD patients a 20-week treatment with as-needed self-administration pharmacotherapy (NTX 50 mg, or an indistinguishable placebo pill). All participants received psychosocial support to improve compliance and were instructed to take the drug 30–60 min before planning or craving to gamble. The primary outcome measure was the total score of the PG-YBOCS. Sixty-nine out of 101 subjects completed the 20-week treatment. Although emotional well-being increased in GD patients with an AA genotype of the *OPRM1* A118G polymorphism, this study was unable to replicate the findings reported in the earlier open pilot study of NTX in GD, i.e. the rates of response did not differ between groups.[43]

3.1.2. Nalmefene

In 2006, Grant et al. published a double-blind, placebo-controlled multicenter study in which 207 subjects with GD were randomly assigned to NMF or placebo. The daily doses of NMF ranged from 25 to 100 mg. The authors reported that NMF was superior to placebo in illness-specific and global outcome measures. Doses from 25 to 50 mg demonstrated superior efficacy than placebo on the primary efficacy measure PG-YBOCS. However, this study did not include SUD and bipolar disorder patients, which are frequently reported among individuals who seek help for GD. Discontinuation rates were higher among those receiving a 50 and a 100 mg daily dose than for those receiving 25 mg. Adverse effects, like nausea, were the most alleged reason for drop out among 50 and 100 mg groups compared to placebo.[27]

Based on their earlier findings, the same group published, in 2010, another placebo-controlled study with NMF in 233 (41.6% women) GD subjects with doses ranging from 20 to 40 mg. Although the NMF group did not fare better than placebo, post hoc analysis indicated that patients who discontinued the trial dropped out before the 20–40 mg regimen was reached. Patients who received at least 1 week of the target NMF dosing regimen (40 mg) did better than those on placebo on the main outcome measure of gambling symptoms (YBOCS modified for GD), particularly on the urges to gamble.[44]

Finally, the effect of opioid antagonists in GD was reviewed in a meta-analysis that also included other pharmacological agents. In this study, Bartley and Bloch selected randomized, double-blind, and placebo-controlled trials examining pharmacological treatments for GD regardless of their pharmacodynamic properties. The authors found that the benefits of antidepressants, antipsychotics (olanzapine), and anticonvulsants (topiramate) were not statistically greater than placebo. In contrast, opioid antagonists were associated with a small, albeit statistically significant improvement in the severity of GD symptoms. The authors listed the small number of studies for each class of the drug and the non-standardized reporting of intention to treat (ITT) data in GD literature as limitations that hampered the interpretation of their findings. The lack of ITT reporting was considered to be particularly problematic, given the high short-term placebo response seen in most GD treatment trials.[45] (Table 1)

3.2. Kleptomania

Kleptomania is characterized by a chronic pattern of stealing behaviors that leads to reward, attempts to self-control, and relief once the patient succumbs to the behavior. Like many other disorders with mixed impulsive-compulsive elements, kleptomania behaviors are maintained despite their adverse consequences.[46] The prevalence of kleptomania in the general population ranges from 0.3% to 0.6%.[47] It affects more women than men and usually begins in adolescence and early adulthood.[48] Kleptomania is also associated with high rates of suicide attempts.[49]

Based on the phenomenological similarities between kleptomania and SUD [11] and on the fact that NTX has shown efficacy in alcohol and opiate dependence, it has been hypothesized that oral NTX would also be effective in reducing stealing behaviors in kleptomania. Indeed, some initial case reports have found NTX to be effective in ameliorating kleptomania symptoms.[50] Also, case studies have shown the effect of NTX in patients with compulsive sexual behaviors and

Table 1. Studies investigating the efficacy of naltrexone (NTX) and nalmefene (NMF) in gambling disorder (GD).

Author	Year	Medication	Sample	Lengh (weeks)	Study design	Primary Outcome Measures	Doses (average)	Results
Kim and Grant	2001	NTX	17	6	Open-label	PG-CGI-PT, PG-CGI-MD[a], G-SAS[b]	157 mg	All outcome measures have shown significant decline, i.e. gambling urge strength, frequency, and duration; gambling thought frequency and duration; subjective distress (G-SAS) and amount of money lost. Also, clinician- and patient-rated CGI scores diminished.
Kim et al.	2001	NTX	83	11	Randomized, double-blind, placebo-controlled.	PG-CGI-PT, PG-CGI, MD[a], G-SAS[b]	188 mg ± 96 mg	Significant decreases in NTX compared to placebo after 12 weeks according to PG-CGI-PT; PG-CGI-MD; and G-SAS.
Dannon et al.	2005	NTX and bupropion	36	12	Open-label	Full response was defined as absence of gambling behavior for 2 weeks	25–150 mg NTX, 150–450 mg bupropion	Full response for 13 of 19 (NTX group) and 12 of 17 (bupropion group)
Grant et al.	2006	NMF	207	16	Randomized, dose ranging, double-blind, placebo-controlled.	PG-YBOCS	Fixed doses: 25, 50, and 100 mg	NMF 25, 50, and 100 mg groups were all significantly superior to placebo. Overall treatment response: CGI improvement score of 2 (much improved) or 1 (very much improved) were considered responders.
Grant et al.	2008	NTX	77	18	Randomized, double-blind, placebo-controlled.	PG-YBOCS	Fixed doses: 50, 100, and 150 mg	NTX group was superior to placebo in PG-YBOCS.
Toneatto et al.	2009	NTX	52	12	Randomized, double-blind, placebo-controlled	Frequency of gambling episodes and frequency and quantity of alcohol consumption	100 mg ± 59 mg	NTX group was not superior to placebo in reducing the frequency of gambling episodes' and on quantity and frequency of alcohol consumption.
Grant et al.	2010	NMF	233	16	Randomized, multicenter, double-blind, placebo-controlled	PG-YBOCS[c]	Fixed doses: 20 and 40 mg	While NMF was not statistically different from placebo in initial analyses, post hoc analyses showed NMF 40 mg group to be superior to placebo. Response was defined as a decrease of ≥35% in the PG-YBOCS
Lahti et al.	2010	NTX	39	16	Open-label	PG-YBOCS	50 mg as needed	A significant decrease in reported obsessive compulsive gambling symptoms
Kovanen et al.	2016	NTX	101	20	Randomized, double-blind, placebo-controlled	PG-YBOCS	50 mg as needed	No differences were found between NTX group and placebo

[a]Pathological Gambling-CGI (patient and clinician rated); [b]Gambling symptom assessment scale; [c]Yale Brown Obsessive Compulsive Scale modified for pathological gambling.

associated kleptomania symptoms [52] and in adolescents with kleptomania.[52]

An open-label study with a small sample (10 subjects) was designed to test the short-term effect of NTX in adults with kleptomania. The author used a specific instrument (Kleptomania Symptoms Assessment Scale) and a global measure of symptom severity (CGI). During the 11-week trial, subjects showed improvement in all measures. The mean NTX dose used to achieve symptom control was 145 mg/day. All the subjects presented reductions in urges to steal and stealing behavior. Nausea was the most common adverse effect.[53]

An 8-week randomized, double-blind trial compared the efficacy of NTX vs. placebo in the treatment of the acute urges displayed by kleptomania patients.[54] Similar to their previous studies in GD, SUD and bipolar disorder patients were excluded from the trial. According to previous evidence suggesting that the doses needed to treat behavioral addictions are two to three times higher than those approved by the FDA to manage symptoms of alcohol and opiate addictions, [51,55] the authors have chosen an NTX dose regimen ranging from 50 to 150 mg/day.

In this study, all the eligible patients were started at 50 mg/day, with progressive increases until 150 mg/day at week four. Twenty-three subjects completed the study (92%). Remission of kleptomania symptoms (defined as a YBOCS modified for kleptomania ≤5) was seen in eight subjects on NTX (66.7%) and in one (7.7%) on placebo. The improvement was noted across a spectrum of illness-specific and global outcome measures. The safety and tolerability profile of NTX in this study were consistent with prior studies and have proved to be favorable.[56] (Table 2)

3.3. Hypersexual disorder and related disorders

Excessive sexual drive (HD) has been recently considered for inclusion in the sexual disorders section of the DSM-5. It has been conceptualized as a non-paraphilic sexual desire disorder with an impulsivity component.[57] HD shares several behavioral features with SUD and other behavioral addictions. The condition is far more common among men, begins in adolescence and early adulthood, and has a chronic course.[58] Like other natural behaviors that are intrinsically rewarding (i.e. eating), sexual behaviors are probably mediated by a system that is under some degree of opioidergic regulation.[59]

Unfortunately, the literature on the use of opioid antagonists in HD is sparse. Raymond et al. described two case reports of individuals with compulsive sexual behaviors treated successfully with NTX.[60] NTX helped suppressing a euphorically compulsive and interpersonally devastating addiction to Internet pornography in a 24-year-old male.[15] Firoz et al. described a 40-year-old man with sexual fantasies and urges toward women's undergarments and associated cannabis and alcohol use disorders, who remained on remission on NTX for at least 11 months.[61] One open study investigated whether NTX (average dose 160 mg/day) could decrease sexual arousal in 21 adolescents participating in an inpatient adolescent sexual offender program. A positive outcome was noted in 15 patients, who remained responders for at least 4 months. is It is worth mentioning that, once treatment was discontinued in 13 patients, symptoms have recurred.[62] More recently, Kraus et al. described the case of a 30 year-old heterosexual male who, after 10 weeks of cognitive-behavioral therapy, still reported urges to engage Internet pornography. Two weeks after prescription of 50 mg/day of NTX, the authors reported a significant reduction in the residual sexually compulsive symptoms.[63]

3.4. Compulsive buying

People with compulsive buying experience repetitive, irresistible, and overpowering urges to purchase goods. In general, the goods are inexpensive and useless.[64] Studies have shown that this condition is more prevalent in women and has its onset in the late teens and early adulthood. The diagnosis requires evidence of severe distress or interference in social, financial, and occupational areas. Pharmacotherapy data are limited and suggests that drugs may be selected according to comorbid conditions. There is only one study with three case reports in which compulsive buying patients were treated with NTX and showed diminished urges to buy. [55,65] There is no literature on the use of NMF for compulsive buying.

3.5. Food addiction and BED

Obesity has become a growing pandemic in developed and developing countries during the last decades. It is associated with increased predisposition for coronary artery disease, congestive heart failure, and sudden cardiac death.[66,67] Overweight and obese individuals differ between each other in their degree of hedonic eating.[68] Excess consumption of palatable food has been shown to affect reward-related brain regions.[69] A study done by Blasi et al. showed that NTX diminished the reinforcement properties of food on previously trained rats.[70] Buck et al. [71] demonstrated that palatable food intake in rats was positively correlated with anticipatory sound conditioning and that NTX can attenuate the positive responses associated with conditioning. Drewenowski et al. [72] demonstrated that naloxone

Table 2. Studies investigating the efficacy of naltrexone (NTX) in kleptomania (KPM).

Author	Year	Medication	Sample	Lengh (weeks)	Study design	Primary outcome measures	Doses (verage)	Results
Grant et al.	2002	NTX	10	11	Open-label	Kleptomania Symptoms Assessment Scale	145 mg	NTX group was superior to placebo in urges to steal and stealing behaviors
Grant et al.	2009	NTX	25	8	Randomized, double-blind, placebo-controlled	K-YBOCS[a]	116.7 mg	NTX group was superior to placebo

[a]K-YBOCS: Yale-Brown Obsessive-Compulsive Scale modified for Kleptomania.

suppressed hedonic responses and reduced sweet and high-fat food intake in human binge eaters but not in non-bingers.

Therefore, it is conceivable to predict that drugs for substance addiction may also be effective in treating overeating in humans. In fact, NTX has been shown to suppress the intake of specific types of foods when administered in association with baclofen, a gamma-aminobutyric acid (GABA-B) agonist.[73] Similarly, the combination of NTX with bupropion, a noradrenergic and dopaminergic reuptake inhibitor, has been associated with greater weight loss than two FDA-approved medications for obesity, i.e. orlistat and lorcaserin.[74] Importantly, the combination of NTX and bupropion has no abuse potential.[74]

BED is an addiction-like behavior characterized by excessive food consumption within a discrete period of time (e.g. 2 h) in an uncontrolled manner that is unaccompanied by compensatory behaviors (e.g. vomiting). Several studies have shown BED to be common in obese patients.[71] One case study suggested NTX (drug A) to be superior to placebo (drug B) in a patient with BED in whom an A-B-A-B design was carried out.[75] This patient remained on psychotherapy along the course of drug treatment. However, the utility of NTX in BED has not been supported by an earlier controlled study.

A randomized, 8-week, double-blind, placebo-controlled study was conducted by Alger and colleagues. Forty-one obese bingers and 28 normal-weight bulimics were selected, but only 33 with BED and 22 with bulimia nervosa completed the study. The subjects were assigned to placebo, NTX, or imipramine. NTX caused a significant reduction in binge duration when compared to placebo in normal-weight bulimic subjects, but not in BED subjects. Further, NTX did not affect binge frequency in both groups. Thus, NTX was ineffective for BED in this study. In contrast, imipramine reduced binge duration when compared to placebo only in BED subjects, but did not affect binge frequency both in BED and in bulimia subjects.[76]

McElroy et al. performed a randomized, parallel-group, fixed-dose, placebo-controlled study to evaluate the effect of ALKS-33 (a new mu-opioid antagonist) in BED subjects. Sixty-nine adults with BED had their diagnoses confirmed by the structured clinical interview for DSM-IV-TR and were randomized to receive either ALKS-33–10 mg (N = 32) or placebo (N = 37) for 6 weeks. At the end point, the authors found a decrease in binge eating episode frequency in both groups, but no significant difference between them in terms frequency or any other measure of binge eating, body weight, or eating pathology.[77] (Table 3)

3.6. Body-focused behaviors

3.6.1. Skin picking

Excoriation (skin picking) disorder is characterized by the repetitive and compulsive picking of skin that results in tissue damage. This impulsive-compulsive condition shares several clinical similarities with SUD, including the failure to stop the behavior despite knowledge of the consequences and a special pleasure while engaging in the activity.[78] Recent community prevalence studies suggest excoriation (skin picking) disorder to affect 1.4–5.4% of the population.[79] Effectiveness of NTX was reported in one case report of pathologic skin picking behavior in an adolescent with Prader–Willi syndrome.[80]

3.6.2. Trichotillomania

TTM is characterized by irresistible hair pulling, resulting in hair loss. The estimated lifetime prevalence is 0.9–4%.[81,82] For a diagnosis of TTM, hair pulling has to be associated with repeated attempts to stop the behavior and clinically significant distress. Hair is most commonly pulled from scalp, eyebrows, and eyelids [1] In DSM-5, TTM is classified as an obsessive-compulsive related disorder. TTM patients present phenomenological similarities with SUD for being frequently associated with an hedonic quality, a trend toward exhibiting hair-pulling behaviors after negative emotional states, urges to engage in the behavior, and relief after pulling hair.[83] TTM first-degree relatives seem to be more likely to have SUD than controls.[84] These similarities have led to the hypothesis that medications used to treat SUD might be effective for TTM.

In 2008, De Souza published an open-label study of NTX for childhood-onset TTM (n = 14). The patients' mean age was 9 years. The dose regimen ranged from 25 to 100 mg with a mean dosage of 66.07 (23.22) mg/day. The TTM assessment was done using the Clinical Global Impressions Scale; urge intensity and hair-pulling frequency were compared. In this study, 78.57% of patients were responders (improvement was defined as a 50% reduction in the urge to pull hair and a 50% decrease in hair-pulling frequency) [85]

A 6-week, double-blind trial by Christenson et al. compared NTX (50 mg/day) and placebo. This study found that a superiority of NTX over placebo was restricted to the NIMH TTM severity scale (p = 0.02). In this study, there was no

Table 3. Studies investigating naltrexone (NTX) and ALKS-33 in binge eating disorder.

Author	Year	Medication	Sample	Length (weeks)	Study design	Primary outcome measures	Doses (average)	Results
Alger et al.	1991	NTX, Imipramine	55	8	Randomized, double-blind, placebo-controlled	Binge duration and frequency	NTX: 100–150 mg Imipramine 50–150 mg	NTX did not reduce binge duration and frequency compared to placebo in BED patients.
McElroy et al.	2013	ALKS-33	62	6	Randomized, double-blind, placebo-controlled	Weekly binge frequency, weight, BMI, waist circumference, Y-BOCS-BE[a], CGI-S, Eating inventory, Food craving inventory, and Beck Depression inventory	ALKS-33 10 mg	A decrease in binge eating episodes in both groups and no difference between groups

Y-BOCS-BE = Yale-Brown Obsessive-Compulsive Disorder modified for binge eating.

Table 4. Studies investigating the efficacy of naltrexone (NTX) in trichotillomania (TTM).

Author	Year	Medication	Sample	Length (weeks)	Study design	Primary outcome measures	Doses (average)	Results
De Souza et al.	2008	NTX	14 (mean age: 9 years)	40	Open-label	Reduction in CGI-S[c], frequency and urge of hair pulling	66.07 mg	At final visit, 8 children showed improvement. Improvement was defined as a 50% reduction in the urge to pull hair and a 50% decrease in hair-pulling frequency
Christenson et al.	1994	NTX	17	6	Randomized, double-blind, placebo-controlled	NIMH TTM severity scale[a]	50 mg	NTX group was superior to placebo.
Grant et al.	2014	NTX	51	8	Randomized, double-blind, placebo-controlled	MGH-HPS[b]	110 mg	NTX group was not superior to placebo.

[a]National Institute of mental health trichotillomania severity scale; [b]Massachusetts General Hospital hair pulling scale; [c]CGI Severity Scale.

improvement according to other outcome measures like NIMH TTM impairment scale, NIMH physician rating scale score, number of hair-pulling episodes, and number of hair pulled.[86]

In 2013, Grant et al. conducted an 8-week double-blind placebo-controlled study with 55 TTM subjects with urges to pull their hair. Patients were randomized to NTX or placebo. The primary measure was the self-reported Massachusetts General Hospital hair pulling scale (MGH-HPS). Secondary measures included the NIMH TTM symptom severity scale and the CGI severity and improvement scales. The authors found no significant difference between patients assigned to NTX vs. placebo on the primary outcome measure.[87] (Table 4)

4. Conclusions

The behavioral addictions are part of a new heuristic construct and share similarities with SUD, such as the development of tolerance, age of onset, similar pattern of comorbidities, natural history, attempts to stop the behavior, and responses to treatment, among others. However, the scientific value of this construct is still under debate. For instance, the concept of 'tolerance' to a behavior is a very problematic one when it comes to using substance and behavioral addiction criteria interchangeably.[88] Patients with GD can play with increasing amounts of money to cover escalating debts rather than to obtain initial levels of reward.[89]

GD is the most studied behavioral addiction and the first to be recognized by DSM-5. Hence, it is understandable that most of the pharmacological research on behavioral addictions included GD studies. Indeed, several trials have been conducted with different classes of drugs.[90] Evidence from opioid antagonists, like NTX and NMF in alcohol and opioid dependence research, has led to the hypothesis of their effectiveness for the treatment of other behavioral addictions.[20,91,92] Despite these studies' limitations, to date, NTX and NMF are the only evidence-based pharmacological treatments for GD.

KPM also shares similarities with SUD, including urges to perform specific behaviors, lack of control over behaviors, and associated attempts to stop performing them. NTX has proved to be effective in ameliorating KPM symptoms. Two clinical trials, one open and one double-blind, showed superiority of NTX as compared to placebo. Thus, there is preliminary evidence suggesting that NTX may be effectively and safely used to treat patients with KPM. Nevertheless, future double-blind confirmatory studies are needed.

TTM and excoriation disorder are listed in the chapter 'Obsessive Compulsive and Related Disorders' in DSM-5, and also share commonalities with SUD. Unfortunately, the primary outcome measures used to evaluate hair pulling in the selected studies were different, and the sample sizes were too small. Future research on TTM should include clinician-administered scale (as hair pulling is many times done without awareness) and larger samples. To date, the quality of evidence does not support the use of opioid antagonists in TTM or excoriation disorder.

Two other conditions included in this study (i.e. compulsive buying and HD) are not listed as valid diagnoses in DSM-5. Although these behaviors are frequent in clinical settings and there is certainly a need to develop treatments to manage them, there is no sufficient evidence supporting the recommendation of opioid antagonists for their management. Although a combination of NTX and bupropion has proved helpful in obesity, there is also no support for the management of food addiction/BED with isolated opioid antagonists.

5. Expert opinion

Psychopharmacology research is among the most challenging areas in medicine as the degree of experimental variability is high, mostly because of imprecise classification and the unpredictable course of many psychiatric disorders. Large trials are needed, since differences in outcomes between different treatments are frequently very small. In fact, although opioid antagonists have been successfully tested in double-blind placebo-controlled studies on the treatments of behavioral addictions (particularly GD and KPM), [90,93–95] future trials with alternative study designs are still needed.

For instance, control groups other than just placebo could be explored. Head-to-head comparisons between NTX or NMF and other active drugs and placebo would be very informative, but can be expensive, take more time to be concluded and also require larger samples. Also, comparative studies with more than one active drug and placebo can determine cost-effectiveness by comparing drug effects and costs.[96] It

would also be interesting to evaluate the issue of dose–response of NTX and NMF, something that could be done by means of fixed-dose studies. Intermittent periods of double-blind placebo treatment would allow to establish how long a drug needs to be continued, as response in psychiatric diseases can take weeks or months. [97]

The identification of particular subgroups of patients with behavioral (and substance) addictions who would be more likely to benefit from opioid antagonists should always be an objective. This could be based on a more refined mental status assessment, as the presence of craving or urges has been suggested to predict increased responses to NTX in alcohol use [38,39] and in GDs (Kim et al., 2001). Although not extensively tested in behavioral addictions, [98] the use of extended-release injectable NTX is also a potentially interesting option in patients proved to be non-adherent to conventional oral formulations.

Current classification manuals like ICD and DSM have proved useful for clinical diagnosis. However, it is well known that categories within these schemes are not able to capture the neurobiological mechanisms underlying dysfunction of specific circuits.[99] Also, the adoption of DSM and ICD may lead to inclusion of patients who are 'neurobiologically' very different in medication trials.[100,101] Several studies suggest that a mis-sense single nucleotide polymorphism (rs179919 or A118G) in the opioid receptor, mu 1 (OPRM1) gene predicts a favorable response to NTX 'G' allele alcohol use disorder carriers [102,103] and there is some preliminary evidence suggesting that the same may hold true for GD.[44] Finally, the differential affinity of NMF for kappa receptors and its resulting effect on the hypothalamic–pituitary–adrenal axis may be associated with a particular effect in a yet to be defined addiction phenotype.[104]

Declaration of interest

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Considerações finais

O tratamento dos transtornos relacionados ao uso de substâncias representa desafio assistencial, clínico e científico. As ideias que relacionaram esta condição à fraqueza moral e religiosa persistiram por muitos séculos, impregnaram o pensamento científico e contribuíram para moldar o preconceito que ainda persiste em nossos dias (VONASCH, CLARK, LAU, VOHS, & BAUMEISTER, 2017; WASSERMAN, 2004). No entanto, nos últimos 25 anos um conjunto de evidências científicas consolidou a noção de que os transtornos relacionados ao uso de substâncias são uma condição clínica específica e uma doença do cérebro, abrindo caminho para que seu tratamento fosse financiado da mesma forma que outras doenças como câncer ou diabetes (VOLKOW et al., 2010).

Nos transtornos relacionados ao uso de substâncias o acometimento inicial de circuitos primitivos e mais ligados à recompensa, se estende para áreas envolvidas em processos cognitivos mais complexos, alterando a memória, a tomada de decisões, a inibição de impulsos e áreas ligadas ao planejamento e estratégia. Estas alterações tornam ainda o indivíduo progressivamente menos resistente ao estresse, causando disfuncionalidade extrema (KOOB & VOLKOW, 2016; VOLKOW et al., 2010). As alterações nos circuitos cerebrais envolvidos nos transtornos relacionados ao uso de substâncias se desenvolvem após anos de exposição a substâncias de reforço e são produto de alterações neuroplásticas bem documentadas (CASTRÉN & ANTILA, 2017; HUANG & REICHARDT, 2001; POO, 2001).

Em 1954 James Olds e Peter Milner pesquisadores da Universidade McGill no Canadá descreveram o circuito de recompensa do cérebro (OLDS & MILNER, 1954). No artigo, Olds e Milner descrevem sua descoberta de que os ratos continuamente pressionam uma alavanca em troca de receber nada mais do que um breve pulso de estimulação elétrica em uma determinada região do cérebro chamada área septal. A constatação de Olds e Milner é relatada pelos autores em linguagem simples:

> Em preparações de área septal, o controle exercido sobre o comportamento do animal por meio desta recompensa é extremo, possivelmente excedendo aquele exercido por qualquer outra recompensa anteriormente usada em experimentação animal. (OLDS & MILNER, 1954, p.47).

Esta descoberta notável gerou a primeira evidência científica dos mecanismos de reforço. Conceitos derivados da psicologia comportamental contribuíram para compreensão dos

transtornos relacionados ao uso de substâncias; como o reforço positivo, ou seja, a introdução de um estímulo associado a um comportamento em particular resulta em maior probabilidade deste comportamento voltar a acontecer (FIELDS, HJELMSTAD, MARGOLIS, & NICOLA, 2007; LADOUCEUR, SCHLUND, & SEGRETI, 2018); e o reforço negativo, ou seja, a remoção de um estímulo aversivo associado a um comportamento em particular resulta em maior probabilidade deste comportamento voltar a acontecer (KOOB et al., 2014). Nos últimos quinze anos, evidências obtidas em estudos de neuroimagem demonstraram que circuitos disfuncionais que envolvem o córtex pré-frontal e a diminuição da população de receptores do tipo 2 de dopamina (D2R) no núcleo estriado têm papel central na gênese e manutenção dos transtornos relacionados ao uso de substâncias (GOLDSTEIN et al., 2002).

A formação de hábito diz respeito a comportamentos que executamos de forma automática e com pouca percepção consciente. Trata-se de uma habilidade adaptativa que permite tomar decisões ou manter um comportamento "poupando" recursos cognitivos (OTTO, GERSHMAN, MARKMAN, & DAW, 2013).

Nossas vidas diárias estão repletas de rotinas automaticamente desencadeadas em que, no mesmo contexto, repetimos comportamentos sem nos darmos conta e sem controle deliberado, enquanto a motivação original para essas ações habituais torna-se cada vez mais irrelevante. Embora os hábitos nos ajudem a operar com eficiência, quebrá-los exige muito esforço, já que são resposta-padrão repetidas em situações específicas. Na epidemia de obesidade e no tabagismo, por exemplo, comportamentos habituais, enraizados e difíceis de mudar estão presentes (WEBB & SHEERAN, 2006).

As ações baseadas em hábitos são controladas pelo estímulo desencadeador, e não pelo resultado da ação, fato relevante para a manutenção e nas recaídas dos transtornos relacionados ao uso de substâncias. A conhecida insensibilidade às consequências do consumo danoso de álcool e outras substâncias de reforço provavelmente reflete, em parte, o aprendizado associativo aberrante determinado pelo abuso crônico e habitual de álcool e outras substâncias (OSTLUND & BALLEINE, 2008).

A transição para uma condição em que o consumo de álcool e drogas não produz mais apenas resultados recompensadores, mas também resultados negativos, assemelha-se a procedimentos de desvalorização de recompensa usados em modelos animais de hábito (BALLEINE & O'DOHERTY, 2010). Evidências em estudos pré-clínicos demonstram que

habituação e comportamentos automáticos precedem os comportamentos análogos às recaídas (KATNER, MAGALONG, & WEISS, 1999).

O transtorno relacionado ao uso de álcool é uma condição clínica complexa, com múltiplas consequências cognitivas e clínicas (CUI et al., 2015), podendo ser definido como um transtorno crônico-recidivante, com consumo compulsivo de bebidas alcoólicas, impossibilidade de limitar o uso e a emergência de um intenso estado emocional negativo que envolve irritabilidade, disforia, ansiedade e estresse (KOOB & LE MOAL, 1997).

Neste estudo foi usada, pela primeira vez, uma escala (HRSF) para medir motivações afetivas (medo e recompensa) e hábito, no mesmo instrumento em cinquenta e oito pacientes em tratamento para transtornos relacionados ao uso de álcool. Adicionalmente, as características psicométricas da escala foram testadas. Também estabelecemos como estas motivações se relacionam com características clínicas e sócio demográficas nesta amostra. Foi demonstrado que comportamentos habituais e automáticos relacionados ao ato de beber estão relacionados positivamente a escores de maior gravidade em pacientes com transtorno relacionado ao uso de álcool, evidências que, até então, só haviam sido obtidas em estudos pré-clínicos (EVERITT and ROBBINS, 2016).

Nesta amostra, menor severidade no uso de álcool e características de personalidade mais relacionadas à impulsividade foram observadas na dimensão ‘recompensa’. Observamos que alguns pacientes obtiveram escores aumentados nas três dimensões (medo, recompensa e hábito). Não observamos relação significativa entre o tempo de exposição ao álcool e hábito.

Foi encontrada correlação negativa entre o número de episódios de tratamento (em regime de internação) tanto para os indivíduos com predomínio de motivações de recompensa quanto para aqueles com preponderância de hábito o que não era esperado, já que os últimos apresentaram maior severidade de TCA. A fim de explicar estes achados novos estudos serão necessários.

Este estudo fornece evidências de que comportamentos automáticos e, portanto, inconscientes, contribuem de maneira significativa para as recaídas e para a manutenção do ato de beber. Estes achados podem contribuir para o desenvolvimento de técnicas de tratamento desenhadas para a prevenção destes comportamentos automáticos, particularmente em pacientes com escores maiores de severidade.

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