WHY ARE SUBSTANCE USE DISORDERS SO DIFFICULT TO TREAT? AN OVERVIEW

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ABSTRACT
Substance-related disorders are chronic and potentially relapsing disorders, consisting in a current public health problem. The goal of this literature review was to provide an overview about the theme, integrating the recent neurobiological findings and to clarify the factors involved in the development of a substance use disorder, which may be specific therapeutic targets.A Medline/Pubmed search was performed with the combination of the following keywords: "substance use disorders" or "substance addiction" or "drug addiction" and "treatment" or "psychiatric comorbidity" or "dual diagnosis" or "cognitive impairment" between 2008 and 2016. The search was restricted to articles published in English. Results suggested that the development of a substance use disorder as well its use pattern may be influenced by several factors. Available therapeutic approaches such as behavioral therapies and pharmacotherapies have shown a modest effect. Treatment of substance use disorders continues to present difficulties and challenges to mental health professionals. There is an urgent need for research on therapeutic options in this field.

Keywords: Substance-Related Disorders; Comorbidity; Therapeutic Approaches.

PORQUE É TÃO DIFÍCIL TRATAR AS PERTURBAÇÕES DE USO DE SUBSTÂNCIAS? UMA VISÃO GERAL

RESUMO
Os transtornos relacionados com substâncias são transtornos crónicos e potencialmente recidivantes, consistindo em um problema atual de saúde pública. O objetivo desta revisão da literatura foi fornecer uma visão geral sobre o tema, integrar os recentes achados neurobiológicos e esclarecer os fatores envolvidos no desenvolvimento de um transtorno de uso de substâncias, os quais podem ser alvos terapêuticos específicos. Foi realizada uma pesquisa na Medline /Pubmed com a combinação das seguintes palavras-chave: "substance use disorders" ou "substance addiction" ou "drug addiction" e "treatment" ou "psychiatric comorbidity" ou "dual diagnosis" ou "cognitive impairment" entre 2008 e 2016. A pesquisa foi restrita a artigos publicados em inglês. Os resultados sugeriram que o desenvolvimento de um transtorno de uso de substância, bem como o seu padrão de uso podem ser influenciado por vários fatores. As abordagens terapêuticas disponíveis, como as terapias comportamentais e farmacológicas mostraram um efeito modesto. O tratamento de transtornos de uso de substância continua a apresentar dificuldades e desafios para os profissionais de saúde mental. Existe uma necessidade urgente de investigação sobre opções terapêuticas nesta área.

Palavras-chave: Transtornos Relacionados com Substâncias; Comorbilidade; Abordagens terapêuticas.

INTRODUCTION

Substance use disorders (SUD) consist in chronic and potentially relapsing disorders with impairment of normal activities. It is considered a public health problem still under investigation. All the substance use disorders have in common an activation of the brain reward system, leading to addictive behaviors[1,2].

Commonly, addiction is defined as a broad range of maladaptive aspects of substance use or other behaviors (compulsive food intake and sexual activity, pathological gambling,

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internet addiction, excessive exercising, compulsive buying and pyromania), leading to clinically significant impairment or distress[3,4].

However, the addictive disorders concept has shown little stability over time, as a result of the increase of clinical research on this issue. In fact, the current edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM)[5]- 5th edition, that was published in 2013, has incorporated new changes in the classification of addictions, generating the "Substance Related and Addictive Disorders" chapter which includes for the first time a non-substance-related, behavioural disorder, the gambling disorder and combines into one new category- "Substance Use Disorder"- the abuse and dependence concepts[6].

Based on DSM-5, SUD are a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems.

There is a large spectrum of illicit and legal substances with addictive potential. Prescription drugs, such as opioids and stimulants are also increasingly being used for non-medical reasons related to SUD[1].

Effective medications are available for nicotine, alcohol, and opioid addictions. Unfortunately, there are not yet FDA-approved pharmacotherapies for the treatment of methamphetamine, cocaine or cannabis use disorders[2].

Behavioral treatments have also been applied in SUD context, namely, contingency management (CM), which abstinence or other targeted outcomes are reinforced with incentives; motivational interviewing (MI), which a specific, nonjudgmental interviewing style is used to enhance motivation and harness the individuals capacity for change; and cognitive behavioral therapy (CBT) which teaches specific strategies and skills to reduce substance use[2]. However, effects remain modest for most behavioral therapies and outcomes vary widely across individuals [2].

Although SUD-related volitional component is widely recognized, more are known about the influence of genetic and environmental factors. In this regard, current researches have suggested that pathophysiological complexity cannot be ruled out when analyzing treatment failure characteristics and chronic evolution[7].

Available studies concerning therapeutic approaches for SUD highlight the lack of guidelines in this field. In fact, several challenges have been identified in the SUD context, particularly related to treatment goals[7,8].

Given the high impact of SUD on morbidity and mortality worldwide, is a priority provide a holistic overview, integrating the recent SUD-related neurobiological findings, to clarify the factors involved in the SUD development, which may be specific therapeutic targets.

MATERIALS AND METHODS

A Medline/Pubmed search was performed with the combination of the following keywords: "substance use disorders" or "substance addiction" or "drug addiction" and "treatment" or "psychiatric comorbidity" or "dual diagnosis" or "cognitive impairment".

Studies published in the English language from January 2008 to December 2016 were evaluated. We excluded studies in other languages and case reports or letters to the editor as well articles without abstracts and studies of other addictions non-substance-related. Thirty-six articles from that search were used.

RESULTS

Heritable influences

The current biopsychosocial model of SUD highlights a complex interaction of genetic (sex differences, ethnicity) and environmental factors (sociocultural diversity, socioeconomic status, stress coping abilities…)[3]. In this way, only in those individuals who present a biological vulnerability to SUD, repetitive exposure to the substance induces long-lasting neuroadaptative changes that further promote drug-seeking behaviors and ultimately lead to persistent and uncontrolled patterns of substance use with tolerance, craving, and withdrawal development[7].

Currently, available studies[9,10] provide a strong evidence for a genetic contribution to the susceptibility to develop a SUD: alcohol use disorder was shown to have a hereditability of 48-66%, nicotine use disorder of 33-71%, cannabis use disorder of 51-59%, opioid use disorder around 23-54% and cocaine use disorder from 42 to 79%, with the lower estimates reported for females.

Based on recent data[9,10], the genetic variation seems also to have an impact on response to SUD-related pharmacotherapy. However, the literature is often inconsistent about whether a particular gene alteration is related to the treatment outcome under observation[10].

Putative candidate genes for SUD-related phenotypes act in a variety of ways: via altered metabolism of substance (alcohol and nicotine metabolic gene variants), via altered function of the substance receptor (the nicotinic receptor, which may alter affinity for nicotine

but may also alter circuitry of reward), and via general mechanisms of addiction (genes such as monoamine oxidase A and the serotonin transporter that modulate stress response, emotion, and behavioral control)[7].

Because dopamine (DA) plays a key role in reward-related behavior, common to all substances, genetic mediators of DA function have been the most extensively investigated. Accordingly, several studies have focused on the connection between the D2 receptor gene (DRD2) and SUD[10].

Preliminary results from family, adoption and twin studies are controversial and characterized by lack of replication, supporting the genetic complexity associated with substance addiction, which derives from multiple sources including incomplete penetrance, phenocopies, variable expressivity, gene-environment interactions, genetic heterogeneity, polygenicity, and epistasis[7]. Although the development and course of SUD is a highly individualized experience, pharmacogenetic researches can give a major contribution to determine why there is such variability in susceptibility, response, and prognosis related to substance use[10].

Gender differences

Over the past few decades, awareness of the importance of male-female differences in addiction has grown and, as a result, an emergent field devoted to characterizing sex differences has and continues to develop[1].

The initiation, use patterns, acceleration of disease course, and help-seeking patterns are affected by gender differences in biologic, psychological, cultural, and socioeconomic factors[4]. It seems that men and women abuse the same substances, but not always in the same ways[3].

Epidemiological studies consistently indicate that men typically use psychostimulants, synthetic cannabinoids and alcohol more often than women[8]. Men are also more likely to use illicit opiate drugs, but women more frequently abuse opioids through initial prescription painkiller use and also report stronger cravings for opiates[3,11].

Men have higher rates of cocaine use disorder, but women with cocaine addiction tend to present a more severe clinical profile. Male cigarette smokers are more likely to have a history of alcohol, cocaine, or marijuana abuse than female smokers who, in turn, suffer from psychiatric disorders (mostly anxiety or depression) more than men. Accordingly, female smokers are more negatively affected by abstinence and experience stronger cravings than men[11].

Women progress through the phases of addiction differently than men: women transition from casual substance use to addiction faster, are more reactive to stimuli that trigger relapse, and have higher rates of relapse then men[1]. Available evidence also indicates that women with SUD may experience more rapid progression through usage milestones-telescoping[12]. This is a term used to describe an accelerated progression from the initiation of substance use to the onset of dependence and first admission to treatment. For opioids, cannabis and alcohol, studies typically reporting an accelerated progression among women. Thus, when women begin substance abuse treatment they typically present with a more severe clinical profile, namely, more medical, behavioral, psychological and social problem than men, despite the less use of the substance and the shorter period of substance use when compared with men[4]. In fact, sex differences related to substance addiction include many issues: impulsivity, compulsivity, decision-making, risk-taking, sensation-seeking, stress responsiveness, psychiatric comorbidity, drug use, craving and relapse[11]. Both intrinsic sex differences in brain organization and activational effects of circulating gonadal hormones have been proposed to account for the observed sex-dependent differences[3].

Enhancing effects of estrogen, and attenuating effects of progesterone, on substance-induced reward have been consistently reported. Similarly, interactions of estrogen with endogenous opioid peptides and the hypothalamic-pituitary-adrenocortical (HPA) axis as well as with DA systems have been proposed as mechanisms underlying estrogen facilitative effects[1,3].

The hormonal status associated with the menstrual cycle has been shown to play an important role in SUD in women. They have greater subjective responses to cocaine in the follicular phase of the menstrual cycle, when levels of estrogen are rising and progesterone levels are minimal. In the luteal phase, when progesterone levels are highest (estrogen levels are also elevated at this time), women report reduced positive subjective effects of cocaine[1]. Studies of nicotine show a potential greater saliency in the luteal phase of the cycle, although the effect of gonadal steroids on responses to alcohol is less clear than for other substances of abuse[4]. Accordingly, the severity of withdrawal symptoms may be greatly different in the luteal and follicular phase of the menstrual cycle[3].

Among substance-dependent subjects attenuated neuroendocrine stress response in women (blunted adrenocorticotropic hormone and cortisol) has been shown following exposure to stress and drug cues. This HPA dysregulation in women may be one key to enhanced vulnerability to relapse in response to negative affect, as it may be associated with greater

emotional intensity at lower levels of HPA arousal[13].

Sex dimorphism in pharmacodynamics (differences in receptor number, binding and signalling downstream from receptor activated) might account for the observations that women are more sensitive to many substances, including those of abuse[3].

Additionally, sex differences in pharmacokinetics (plasmatic protein binding of drugs, volume of distribution, drug transport and metabolism) might explain why women are more often overdosed[3].

Evidence also suggests that gender influences the course and treatment of SUD. In general, women are less likely to seek treatment for their addictive disorder than men[1]. However, once women begin treatment, gender itself is not a predictor of treatment retention, completion, or outcome[4]. In addition, women who start substance abuse treatment programs have a more severe addiction syndrome and higher prevalence of co-occurring mental health disorders[1].

Lifetime rates of mood and anxiety disorders are significantly higher among women than men, with and without SUD[4]. In relation to other psychiatric disorders, eating disorders (EDs) are estimated to be 2 to 3 times higher in women than men. Among women with SUD, high rates of EDs, in particular the purging subtypes of bulimia, have been reported[4].

Among treatment-seeking women with SUD, rates of physical or sexual abuse are high, ranging from 55% to 99%, with many of these women manifesting trauma-related symptoms consistent with a diagnosis of posttraumatic stress disorder[4].

Most investigations of sex differences in treatment-seeking populations have important limitations, because they often focus on single substances and typically do not account for significant polysubstance abuse[12]. Additionally, to date, most substance abuse treatment models have been designed for men and based predominantly on male norms. However, gender-specific interventions that are designed to deliver information and services tailored for women are beginning to emerge in response to mixed-gender programs, which often fail to address women's specific needs, such as childcare assistance, pregnancy, parenting, domestic violence, sexual trauma and victimization, psychiatric comorbidity, housing, income support, and social services[4].

Dual disorders

Epidemiological and clinical studies find that SUD and other psychiatric disorders are highly comorbid (a condition referred to as "dual" or "co-occurring" disorders). Therefore,

mood, anxiety, and personality disorders need to be considered by substance treatment specialists to achieve successful intervention[3,8,14,15].

Substance users with comorbid psychiatric disorders report greater psychosocial and medical problems and poorer prognosis than those without[16]. Response to treatment in patients with this comorbidity is difficult, regarding the high rate of recurrence and non-compliance[17].

At present, great importance is given to distinguish between independent and substance-induced disorders, as they may have different clinical courses, treatment strategies and outcomes. However, few studies have differentiated these psychiatric disorders[16].

A recent study[16] with illicit substance users recruited from different treatment and non-treatment settings showed that almost 42% of these patients met criteria for a lifetime Axis I disorder other than SUD and 36% of which were substance-induced. Being female, recruited from an out of treatment setting and the number of SUD, are risk factors for substance-induced disorders[16].

Personality disorders (PDs) are among the most prevalent comorbid disorders in treatment-seeking patients with SUD and did not remit with its treatment. Accordingly, when studies included all SUD samples, the prevalence of PDs ranged between 35-91%, being antisocial and borderline PDs the most prevalent[18].

Among those with alcohol, cannabis and nicotine use disorders, 27.6%, 32.4% and 20.3%, respectively, had more than one PD[14].

SUD patients with PDs differ from those without PDs. They are younger, have lower levels of education, are less likely to be married, are more likely to abuse illegal substances, have more psychopathology (including anxiety and depression), are more impulsive, and less satisfied with life. Thus, SUD patients with PDs have different treatment needs and poor course of axis I disorders[18,19].

Among injecting substance users accessing a syringe program, cluster A PDs were associated with substance use severity, presence of an Axis I mental health disorder and poorer social quality of life. Cluster B PDs were associated with increased substance use severity, whereas borderline PD was specifically associated with poorer quality of life on psychological and environmental domains. Overall, Cluster C PDs had the strongest associations, including severity of psychological distress, polysubstance use, presence of an Axis I mental health disorder, and lower quality of life on the physical, psychological and environmental domains[20].

Anxiety disorders were more prevalent in SUD patients with PDs than in those without. Almost 70% of SUD patients with PDs had an anxiety disorder, most often social phobia. The

high prevalence of social phobia in SUD patients and the high prevalence of SUD in patients with social phobia indicate that patients with this disorder may have a disposition towards excessive SUD. The combination of social phobia and PDs seems to increase the risk of early SUD onset[18].

Three PDs (antisocial, borderline and schizotypal), significantly and robustly predicted the persistence of the SUD, even after controlling for many other potentially negative prognostic indicators[14].

Antisocial PD and the persistence of alcohol, cannabis and nicotine disorders are consistently reported, suggesting that some SUD and antisocial PD form part of a unidimensional domain of psychopathology often referred to as the externalizing domain[14].

Many treated SUD patients with antisocial PD have other PD and aspects of SUD-related outcomes may differ between SUD antisocial patients with and without other PDs[14].

In what concerns to borderline PD, among illicit substance users, those with this PD were more likely to have substance-induced and independent psychiatric disorders[16]. Its presence is a robust predictor of the persistence of alcohol, cannabis and nicotine use disorders even after controlling for many other potential confounders[14].

The strong relationship between schizotypal PD and SUD is drawing increased attention. Given the interest in cannabis use as a risk factor for schizophrenia and the connection of schizotypal PD to schizophrenia, several studies examined the relation between cannabis use disorder and schizotypal symptoms and have found that these symptoms can precede cannabis use disorder, giving support to a temporal association not only explained by later cannabis effects. The relationship between schizotypal PD and nicotine is also receiving increasing attention[14].

Persistent alcohol use disorder was also predicted by narcissistic PD. Obsessive-compulsive and schizoid PDs were not associated with persistent alcohol or cannabis use disorders, but seem predict persistent nicotine use disorder[14].

Recently, in patients with SUD, more attention has been focused on specific personality trait effects[8].

Personality traits are considered risk factors for SUD, which also, in turn, impact individuals' traits. Furthermore, there is increasing interest in developing treatment approaches that match an individual's personality profile[8].

The Five Factor Model of personality presents key-traits closely implicated in SUD (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness).

Individuals who are prone to negative emotions (high neuroticism), those who are antagonistic and hostile (low agreeableness), and those who are disorganized and undisciplined (low conscientiousness) are more likely to have a SUD than those who score on the opposite pole of these traits[18]. Accordingly, seems to exist an association between high neuroticism scores and cocaine-induced psychosis, independently of other consumption variables[22].

Specific personality traits are in part an antecedent, not just consequence of SUD[18,21]. Accordingly, adolescents are at greater risk of developing a SUD by age 20 if they score high on negative emotionality, a trait akin to neuroticism, or low on constraint, a trait akin to conscientiousness[18,21].

Patients with severe psychotic disorder use illicit substances more than the general population. SUD in these patients have negative consequences, including recurrence of disorder, repeated admissions, homelessness and violence. Using substances such as lysergic acid diethylamide, cannabis and amphetamines produce schizophrenia like symptoms that complicate the diagnosis and worsen the prognosis[17]. In fact, three types of relations may occur between substance use and psychosis: substance use may lead to psychosis onset (either a cause or precipitant factor), substance use after onset of psychosis and substance use beginning concurrent with psychosis onset[17].

Mood disorders and SUD commonly co-occur[23,24]. The lifetime prevalence rate of any bipolar disorder and any SUD is 47.3%[23].

In bipolar patients, comorbid SUD are associated with poor treatment adherence, longer and more frequent mood episodes, more mixed manic-depressive episodes, lower functional recovery, even during abstinence, more utilization of emergency services, more hospitalizations and often with an increased impulsivity and suicide compared with bipolar patients without SUD, suggesting that SUD may be a marker rather than a determinant of bipolar illness severity[24].

Comorbid SUD is also high in major depression, with lifetime rates of 40.3% for alcohol use disorder and 17.2% for any SUD[23]. Available data shows that among patients with major depression, those with ‘atypical’ depressive symptoms (increased sleep and eating) were more likely than others to have SUD[14.]

In early adolescence, depression symptoms are associated with increased likelihood of lifetime use of cigarettes, marijuana, alcohol, inhalants, prescription painkillers, and any substance[25].

Individuals with adolescent and young adult-onset SUD had increased odds of

developing a secondary mood disorder. Therefore, these patients should be closely monitored for both positive and negative mood symptoms. SUD treatment and aftercare offer opportunities for the early identification of secondary mood disorders[26].

Clinical differences between independent (primary) and substance-induced (secondary) mood disorders in patients with substance use are insufficiently studied[24,27]. Patients with substance-induce major depressive disorders (MDD) show improvements in their mood disorder by staying abstinent. Substance-independent MDD cannot be expected to remit with abstinence in SUD patients[27].

Consistent findings are the higher prevalence and severity of substance-independent MDD in females than in males. Additionally, substance-independent MDD with adolescence onset constitutes a risk factor for subsequent SUD and substance-induce MDD[27].

Patients with co-occurring mood and SUD are difficult to treat[20]. A traditional approach to the diagnostic dilemma is to withhold pharmacologic treatment for depression for a period of time after abstinence is established in order to determine whether, and to what extent, mood symptoms are attributable to substance use[24].

However, there are a growing number of clinical programs for patients with co-occurring disorders that integrate treatment for SUD with treatment for another psychiatric disorder. Nonetheless, little empirical work has been done to provide guidelines for prescribing pharmacotherapy for patients who have both mood and SUD[23].

In fact, in cases where the mood disorder is solely a result of alcohol or substance use, the question arises as to whether a medication for a mood disorder would have any therapeutic impact beyond what abstinence from alcohol and drugs would achieve, since in many cases mood-related symptoms will spontaneously dissipate with reduction or cessation of substance use. In such cases, the use of antidepressant pharmacotherapy would likely be unnecessary, costly, and burdensome to the patient[23].

Generalized anxiety disorder (GAD) and SUD are highly comorbid, associating with high overall vulnerability for additional psychopathology, particularly in the externalizing spectrum, a poor psychosocial outcomes, including higher rates of hospitalization, disability, functional impairment, higher use of alcohol and drugs to relieve anxiety symptoms and inferior GAD and SUD treatment outcomes[28,29].

Recent investigations found a considerably high rate (30%) of lifetime bipolar disorder among those with GAD-SUD. This subgroup of bipolar individuals is likely to suffer from a more severe psychopathology and burden since the comorbidity of anxiety disorders and SUD

in bipolar individuals have been consistently associated with worse prognosis and higher rates of suicide attempts[29].

Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable (70%) neuropsychiatric disorder with typical onset in childhood. Furthermore, in a substantial proportion (75%) of cases, ADHD symptoms do not remit in childhood/adolescence and continue into adulthood[13].

Research has shown that those with ADHD have an increased risk for addiction disorders like alcoholism and substance use disorders. Both ADHD and addictions have also been associated with personality traits such as impulsivity, reward seeking, anxiousness, and negative affect[13].

The available literature found that substance and alcohol uses were about six times more likely in cases with ADHD than in controls, and that females had a significantly higher risk than males. Additionally, research also indicates that the comorbidity of SUD and ADHD is associated with greater social and psychiatric impairment[13].

Cognitive impairment

The full extent of drugs' impact on cognition is not yet known. Research indicates that addicted individuals have changes in brain regions including the striatum, prefrontal cortex, amygdala and hippocampus that are involved in essential cognitive functions, particularly learning, memory, attention, reasoning, and impulse control[30].

It is consensual that many substances produce cognition-related withdrawal symptoms that may make abstinence more difficult. These include deficits in cognitive flexibility for cocaine; deficits in attention and impulse control for amphetamines; deficits in cognitive flexibility for opioids; deficits in working memory and attention for alcohol; deficits in cognitive flexibility and attention for cannabis and deficits in working memory and declarative learning for nicotine[30]. While withdrawal-related cognitive deficits are often temporary, long-term substance use can also lead to lasting cognitive decline. The nature of deficits varies with the specific substance, the environment, and the user's genetic makeup[30].

Multiple studies have reported that chronic substance use, especially cocaine, methamphetamine, cannabis and cigarette smoking are associated with deficits in cognitive functioning, including in decision-making, response inhibition, planning, working memory, and attention[30,31]. In relation to cannabis, the most widely used substance in the world, both acute and chronic exposure are associated with dose-related cognitive impairments, most consistently

in attention, working memory, verbal learning, and memory functions. These impairments are not completely reversible upon cessation and how long these deficits persist is not yet known[30,31].

Neuropsychological impairment among patients with SUD contributes to poorer treatment processes and outcomes including treatment motivation, readiness to change, self-efficacy, insight, coping skill acquisition, use of commitment language, treatment attendance, aftercare attendance and less abstinence[32]. However, neuropsychological assessment is typically not an aspect of evaluation in SUD treatment programs because it is prohibitively time and resource consuming. In this regard, recent investigations suggest the clinical utility of a brief screening measure, the Montreal Cognitive Assessment (MoCA), in identifying cognitive impairment among SUD patients[32].

The cognitive assessment is nothing easy in clinical practice. Comparing substance users and healthy controls on cognitive function requires careful consideration of many potential confounds: education, intelligence quotient, and other psychiatric comorbidities or length of abstinence within substance users, suboptimal cognitive assessment tools and small sample sizes[31].

The literature highlights the importance of considering past and present cognitive function when treating SUD-patients, as substance-related cognitive changes may bias patients toward responses and actions that contribute to the cycle of addiction. Even among users of the same substance, cognitive impacts will differ depending on variations in environmental factors and genetics. Understanding the influence of an individual's genetic background on the manifestation of symptoms is a critical area for future research[30].

Despite evidence of a strong association of cognitive deficits in SUD populations, particularly in their most severe form, the clinical implications of these findings has received limited attention, perhaps due to the subtle nature of many of these deficits, variability across individuals and observations that at least some of these deficits may be reversible following cessation of substance use. However, several studies suggest that cognitive deficits are not reversible after short-term abstinence[31].

If cognition influences SUD outcomes and general functioning, cognitive enhancement will serve as an important treatment target, regardless of whether cognitive impairments in addicted populations reflect persistent brain dysfunction secondary to chronic substance uses; acute substance effects; short-term withdrawal effects; pre-existing vulnerability factors for addiction; or, perhaps most plausibly, a combination of several of such factors[31].

Although several cognitive-enhancing pharmacological treatments are being assessed for clinical use, it remains to be determined whether these therapies can reduce substance use through improvement of selective cognitive functions. The promising cognitive enhancing pharmacotherapies for SUD include cholinergic medications (galantamine, varenicline), monoamine transporter inhibitors (modafinil, methylphenidate, atomoxetine), alpha$_2$-adrenergic agonist (guanfacine), glutamatergic medications (memantine, D-cycloserine, minocycline) and behavioral approaches, namely CBT, general cognitive training, attentional retraining and cognitive bias modification[31].

Among behavioral approaches, computerized cognitive rehabilitation that is designed to enhance cognitive skills though exercises that target problem-solving skills, attention, memory and abstract reasoning, has demonstrated some promise in residential settings[31].

Most behavioral treatments for SUD are predicated on the ability of the patient to attend to treatment, understand interventions and behavioral change strategies and be able to implement them. Intact cognitive functioning may be particularly crucial for more complex approaches such as CBT that emphasize cognitive re-training and learning of new behavioral skills[31].

DISCUSSION

The best therapeutic approach for SUD patients remains yet a challenge.

In the last years, there has been significant progress and expansion in the development of evidence-based psychosocial treatments for SUD. These include CBT (with relapse prevention), CM, motivational enhancement and brief interventions[33].

However, there are no effective pharmacotherapies for some SUD and abstinence rates, following behavioral therapies, have been modest[31]. Therefore, scientific investment for effective treatments related to SUD is a currently priority.

Perhaps the best treatment needs to be individualized in each case either at pharmacological and psychological level. The identification of specific genes and environmental factors that change the vulnerability and ability to recover could represent a first step to develop an etiologically based nosology and to individualized treatment[7].

Identifying consistent predictors of SUD in prospective studies has also been difficult. Some factors, referred in the literature, include family history of SUD and Axis I disorders such as major depression and anxiety disorders. However, not all studies have had consistent findings on these relationships[14].

The majority of data on treatments for SUD suggests that combinations of behavioral and pharmacotherapies may be more effective than single approaches. Combining existing pharmacological and behavioral addiction therapeutics with cognitive enhancement could similarly improve treatment outcomes[31].

Research on comorbidity offers avenues to better understand etiology, natural history, treatment setting, and, ultimately, more moving towards an effective treatment and prevention efforts for substance and psychiatric disorders[19]. However, concerning dual disorders, there is a paucity of treatment researches[34].

Effective treatment for comorbid conditions must combine different therapeutic approaches (psychotherapy, pharmacotherapy and behavioral treatments), once together can increase therapeutic efficacy by exerting a synergistic impact[15].

Atypical antipsychotics, including clozapine, are preferred in patients with comorbid psychotic disorders. Apart from valproate, preliminary findings suggest the effectiveness of quetiapine in bipolar patients with SUD. Selective serotonin reuptake inhibitors in combination with anticraving agents (sertraline and naltrexone combination) were found useful in patients with major depression and alcohol dependence. Effectiveness of atomoxetine is yet to be established in patients with comorbid adult ADHD with respect to decrease in substance use[34].

Based on previous studies, maybe the best treatment of SUD patients with simultaneous psychiatric disorders (induced or not) requires high-intensity and integrated interventions-Integrated Dual Disorders Treatment[15,35]. This therapeutic approach often involves an interdisciplinary team, including social workers in various roles and in a mental health setting and uses multiple interventions, including assertive outreach, group treatment, stages of treatment, and motivational approaches to address psychiatric and substance abuse issues concurrently[15,35]. In fact, only an integrated treatment modality has been found to be consistently better than the treatment of individual disorders at separate settings[15].

Regarding practical implications to SUD patients, this overview highlights how difficult can be to treat these patients and the need to individualize the treatment, since different factors are involved in each case and cannot be ruled out. Therefore, standard therapeutic interventions for some conditions (abstinence and craving...) should be considered in combination to other more individualized.

CONCLUSIONS

SUD are a worldwide public health problem and their treatment continues to be a challenge. Available studies pointed out that the therapeutic approach should be holistic, looking at the various factors involved in SUD (intrinsic and extrinsic factors as well the nature of the addictive substance).

Perhaps the best therapy has to be individualized in each case at both pharmacological and psychological stances.

Further studies are needed in order to get a better knowledge of all the factors involved in SUD, developing more effective therapeutic approaches, improving the existing ones and avoiding the chronic evolution of this psychiatric disorder.

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