

## Case Series

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# Cariprazine as an anti-impulsive treatment in a case series of patients with HIV and chemsex practices

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## Abstract

**Purpose:** Unprotected sex in men who have sex with men is considered the main current mechanism of HIV infection in Western-culture countries. Chemsex refers to the use of different drugs and substances before or during sexual activities to enhance the sexual experience. Men who have sex with men are a population at risk for chemsex practices and chemsex has also been associated with an altered perception of risk, which leads to increased risk of sexually transmitted diseases, such as HIV. Cariprazine, a novel antipsychotic agent has shown promising results in animal models of substance abuse.

**Design/methodology/approach:** We present three patients diagnosed with VIH and chemsex practices who received off-label treatment with cariprazine in addition to their usual medication regimens.

**Findings:** All of the patients showed an improvement in the risk domain of the Maudsley Addiction Profile, a brief interviewer-administered questionnaire that assesses behavioral aspects in patients with substance abuse. None of them referred side effects. Research limitations/implications - Cariprazine could be a therapeutic weapon for the treatment of HIV patients who engage in chemsex practices. Originality/value - This is the first study to examine the off-label use of cariprazine in a population of HIV and chemsex users' patients.

**Keywords:** HIV; chemsex; slamming; MSM; cariprazine; maudsley addiction Profile.

## Introduction

According to the UNAIDS (Joint United Nations program on AIDS/HIV), in 2020, there were 37.7 million people in the world living with Human Immunodeficiency Virus (HIV) and 1.5 million becoming newly infected [1]. The current HIV rate in Spain is 7.46 per 100,000 inhabitants [2]. Unprotected sex in Men who have Sex with Men (MSM) is considered the main current mechanism

of HIV infection in Western-culture countries like Spain [2] and the US [3]. Previous studies have showed that MSM experience greater physical and psychological distress [4]. Therefore, the group of MSM with HIV is a priority for prevention and intervention programs, especially the group between 25 and 34 years old, where the rates of HIV transmission are higher [2].

Sexualized Drug Use (SDU) refers to sexual activities whilst

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under the influence of a wide range of drugs and substances, being chemsex a particular form [5]. Chemsex, coming from the contraction of “chemical sex”, has been documented since 2013 [6]. Chemsex users take one or more illegal psychoactive substances immediately before or during sexual activity to facilitate, influence sexual perception, enable long-lasting sex sessions, and/or intensify sexual experience, sometimes over several days, or with several partners simultaneously [6]. Five different substances have been typically associated with chemsex: amyl nitrates (“poppers”), methamphetamine (“crystal meth,” “T,” “Tina”), mephedrone, Gamma-Hydroxybutyrate/Gamma-Butyrolactone (GHB/GBL) (“liquid ecstasy”), and ketamine [7]. Motivation for substance use is based on the psychological and physical effects these substances have, so it must be clearly differentiated from sex that occurs accidentally after substance use [8]. Although not exclusively, previous studies identified primarily MSM as the population at risk for chemsex [9]. Chemsex is associated with an altered perception of risk, which leads to increased risk of Sexually Transmitted Diseases (STD), such as HIV [10] and poorer mental health [7]. For this reason, chemsex stands as a major concern for Public Health policies worldwide [10].

Cariprazine is a new-generation antipsychotic that introduces a novel mechanism of action, having the highest affinity for the Dopamine-3 Receptor (D3R) in addition to interacting as a partial agonist with the Dopamine-2 Receptor (D2R) and the serotonin-1A Receptor (5-HT1AR) [11]. Cariprazine is currently approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA) for treating schizophrenia in adults; and approved by the FDA for treating acute mania,

mixed or depressive episodes associated with bipolar I disorder [12]. Cariprazine, through its partial agonism for D2R has shown promising results in animal models of substance abuse [13]. Even more, through its high affinity for D3R, which is widely distributed in the limbic system; including the nucleus accumbens, responsible for the reward and motivation circuit, cariprazine may constitute a novel therapeutic target for addictive substance use [14]. In fact, cariprazine has proven to be effective in two cases of patients diagnosed with schizophrenia and comorbid substance abuse [15].

The Maudsley Addiction Profile (MAP) [16] is a brief interviewer-administered questionnaire that assesses basic behavioral aspects through 60 items in patients treated for substance abuse in four domains: 1) substance use; 2) health risk behavior (injection and risky sexual behavior); 3) health symptoms (both physical and psychological); 4) personal and social functioning. This interview has been validated in Spain and its main purpose is to collect standardized information on basic aspects of the patient’s behavior and problems, throughout the different phases of treatment (baseline, follow-up and treatment completion) [17].

In this case, series, we present 3 patients diagnosed with VIH and chemsex practices who received off-label treatment with cariprazine in addition to their usual medication regimens and were assessed with the risk domain of the MAP, both at baseline and during follow-up. All patients gave consent for the off-label treatment with cariprazine and benefits and possible side effects were explained and monitored closely.

**Table 1:** Summarizes sociodemographic information, variables concerning HIV, drug use and MAP, both at baseline and during follow-up (4 weeks).

Sex	Age	CD4	HIV	HIV treatment	Drugs	MAP pre-treatment	MAP post-treatment					
						Diagnosis	% DI	TSN	TUS	%DI	TSN	TUS
Male	28	962	U	D/C, L, S	GHB, Methamphetamine, M	Panic disorder	38	0	5	28	0	3
Male	44	118	U	B/E/T	Cannabis	Adjustment disorder	0	0	3	0	0	2
Male	49	976	U	D/T/E	Cocaine, Popper, M	SUD	62	3	8	58	1	6

**Note:** CD4: Cluster of differentiation 4 (CD4/mm<sup>3</sup>); HIV: Human Immunodeficiency Virus (copies/ml); U: Undetectable; HIV treatment: Human Immunodeficiency Virus Treatment; D/C: Darunavir/Cobicistat; L: Lamivudine; S: Silymarin; B/E/T: Bictegravir/Emtricitabine/Tenofovir Alafenamide; D/T/E: Dolutegravir/Tenofovir /Emtricitabine; D: Drugs: GHB: Gamma Hydroxybutyrate; M: Mephedrone; SUD: Substance use Disorder; MAP pre-treatment: Maudsley Addiction Profile pre-treatment; % DI: % Days Injected; TSN: Times Shared needles/syringes; TUS: Times Unprotected sex; MAP post treatment: Maudsley Addiction Profile Post Treatment.

### Case presentations

Table 1 summarizes the 3 cases, including sociodemographic variables, HIV related variables such as antiretroviral treatment or cell count and the risk domain of the MAP before and after cariprazine treatment.

#### Case 1

Brazilian 28-year-old male, working as an escort and pornographic actor, who was referred to the consultation due to symptoms of anxiety and depression associated with chemsex practices. He was diagnosed of HIV and was on antiretroviral therapy with good immunovirological control and a history of

syphilis and proctitis and with no prior psychiatric history. He reported intense panic attacks on a daily basis, at least, for the past 3 months. He had been anxious walking on the street, afraid of people surrounding him: “I am aware that there are people who are talking and looking at me, although I know that is not like that”. “I feel discomfort, I feel dizzy, I’m tense, my mouth dries up, I feel pressure on the back of my neck, my shoulders are heavy, my body is stiff and I’m very tired”. He also described traumatic events throughout his life, such as the diagnosis of HIV (he was infected by a partner), being kidnapped by his own father when he was 4 years old, the death of a friend from COVID-19 at the beginning of the pandemic or, most recently, being drugged at a party. He had started to develop post-traumatic stress disorder symptoms related to that specific

event which appeared to be in complete remission at the initial evaluation. He acknowledged that he was using anabolic steroids to enhance his musculature and GHB, mephedrone and metamphetamine to have sex with other men, both in his private life and during his usual work, as a way to uninhibited. He found it very difficult to stop these behaviors, yet knew he was aware that he was paying a high price, as chemsex was having an important and negative impact on his well-being. He could relate his panic attacks to the use of drugs to have sex with other men and how he felt about it afterwards. Cariprazine, at low doses, was considered, specially based on a low profile of adverse events and good tolerability. His main concern were sexual side effects and for this reason, Selective Serotonin Reuptake Inhibitors (SSRIs) and other antidepressants were ruled out. He started taking 1.5 mg/daily. During follow-up, he reported a less impulsive behavior in general, which resulted in less unprotected sex and less drug injection. This led to a significant improvement in his anxiety levels, with a significant impact on his autonomy and general sense of well-being. He did not report side effects with the medication.

### Case 2

Spanish 49-year old male, who first came to consultation to treat his recreational drug use. He was diagnosed and treated for HIV and had a history of treated syphilis. He had been admitted to a detoxification and treatment center for addictions in the past and had irregular follow-up with poor adherence to specific resources for the treatment of addictions. He was currently unemployed, but had been working in a school as a teacher. He was fired for multiple unexcused absences from his job. He referred that he had a great conflict between his homosexuality and his personal beliefs and, for that reason, he resorted to slamming (drug injection) and chemsex practices. He described that the use of drugs “helped” him “be the person he truly thought he was”. He was currently using inhaled cocaine, occasional mephedrone and popper. He reported a feeling of “being blocked” and “unable to move forward”, because he was using drugs on a regular basis and admitted that it would be very difficult for him to stop. He felt guilty and ashamed for not being able to control substance use and chemsex practices. “My problem now is that I am blocked, I would have a life ahead, I could live my homosexuality with normality, do normalized things, but drugs keep me away from it”. He referred he fluctuated between the craving to use drugs and the depression due to the slump he felt afterwards. He had depressed feelings of loneliness and isolation. He would like to be able to change the situation, although he did not know how to do it, as he had the feeling that “all therapies have failed, I am the one who does not change”. Off-label treatment with cariprazine was discussed with him. He started taking 1.5 mg/daily, and after 4 weeks with good tolerance but little results, it was increased to 3 mg/daily. Motivational work was carried out to change the perception he had about substance use after which he was also recommended to attend specific therapy to treat his substance addiction.

### Case 3

Spanish 44 year-old male, severely immunosuppressed, who was referred to consultation for anxiety and depression. He was diagnosed of HIV and had no prior psychiatric history. He was currently unemployed and living alone, although he previously lived with his ex-partner and the mother of their

two children. He reported having a bad relationship with his ex-partner, but a good relationship with the children’s mother and his sons. He was currently engaging in chemsex practices with other men, though the only substance he claimed he was using was cannabis. He referred his symptoms started several weeks before the consultation, with an increase in stress and workload. He described the feeling that the bonds he had were “weakening” and that he was distancing from his friends. Overall, he described an important apathy, but could not point out if it was related to the use of cannabis. He acknowledged though, that smoking cannabis helped him to “escape from his reality”. He also recognized low tolerance for frustration and poor emotional management. He also felt as if he had “no energy”. He was more agitated at night, with worse night’s rest. He also acknowledged difficulties in self-care and following schedules and daily routine. He related all of these negative feelings with not being able to stop engaging in unprotected sex with other men. He admitted that if he could control his cannabis use, it would be easier for him to stop engaging in risky sexual behaviors. Cariprazine, at low doses consisting of 1.5 mg/daily was prescribed. After four weeks of treatment, he expressed lower anxiety levels and better mood.

### Discussion

The social and psychobiological constructs that explain the need and use of substances for sexual intercourse have yet to be elucidated. However, MSM are at risk for chemsex and slamming practices. Slam is a part of the chemsex area defined by the intravenous use of psychostimulants in a sexual context [18]. One of the main explanatory approaches is the concept of “minority stress”, which can be defined as the relationship between minority and dominant values and resultant conflict with the social environment experienced by minority group members [19]. In a way, this could partially explain why MSM practice chemsex in a predominantly heteronormative society. The collision between the more prevalent heteronormative ideas and individual sexual preference would create a chronic stressor through time and perceived stigma as a result of being part of a minority that is counteracted by substance use [7,20]. A retrospective study in the Taiwan area of HIV patients receiving antiretroviral therapy found that recreational drug use was significantly associated with younger age, longer HIV infection and poor antiretroviral therapy adherence [21]. In our sample, patients described using illicit drugs to have sex as a way to break inhibitions in relation to sexual behaviors or as a way to escape their daily routine. Nevertheless, all of them referred good adherence to HIV treatment.

Chemsex is a growing problem in the last decade [10] that has physical and psychological consequences and great cost [4,7]. A survey in German found that people with chemsex practices had significantly higher mean scores for depression, anxiety, and somatization compared to the non-chemsex group, even though the effect size was small [7]. Specifically, the rate of clinically significant depressive symptoms was twice that of the general population (11.9% vs 6.1%) [7]. Interestingly, this study also found that the lifetime suicide attempts prevalence was also higher in the chemsex-group [7]. A study analyzing chemsex practices during the social distancing period caused by the COVID-19 pandemic in Brazil and Portugal found that MSM kept engaging with chemsex practices, in spite of following the recommendations of the health authorities [22]. A different study analyzing MSM with HIV who practice chemsex in Spain

found that these patients participated in more risky sexual practices (more frequent condomless sex with occasional partners) and had a poorer quality of life [23]. This growth in chemsex practices might be due to an increase in the use of apps that offer the immediate possibility of meeting many people in a short period [24]. Chemsex has been associated with health risk behaviors, such as drug injection (slamming) and risky sexual behavior (condomless anal intercourse and a greater number of partners, as well as with a greater likelihood to be HIV positive) [5] and higher rates of STIs and Hepatitis C infections (HCV) [25]. Unsafe injection practices by MSM in sex context (slamming) are of particularly significant concern because they can also facilitate HIV transmission, HCV transmission, and multiple Sexually Transmitted Infections (STIs) [18]. A qualitative study investigating drug use and harm reduction techniques among Swedish MSM described broad range of both positive and negative aspects associated with drug use [26]. Participants described a balance between risk, safety and pleasure developing strategies to minimize short term and long-term harm: controlled intake, knowledge about drug use, pre-decided behavior rules and strategies for handling overdoses [26].

Although cannabis has not been typically included as a substance for chemsex practices, we described the case of an HIV patient, severely immunosuppressed, who used it during sexual intercourse with different partners. A previous study in England highlighted among its recommendations that health care providers pay attention to the high prevalence of cannabis use, in addition to other drugs, that existed in heterosexual patients who attended HIV centers and, in particular to the relationship between cannabis use and risky sexual behaviors and poor mental health symptoms [27].

Another paramount matter of concern in chemsex users would be adherence to HIV treatment. Alcohol and substance abuse have been proven to be important factors related with lower HIV treatment adherence [28]. Recreational drug use is also related with low disease awareness and with lower risk perception [29] and both contribute to enhance or prolong sexual intercourse (even with multiple partners) which often lead to unprotected and/or prolonged sex (which implies a higher risk of abrasions and tears in the mucosa). Even more, Drug-Drug Interactions (DDI) between recreational drugs and antiretrovirals can lead to potential toxic and/or fatal effects or affect the plasmatic concentrations of antiretroviral therapy [30]. Besides, previous studies have pointed out that chemsex practices in people with HIV and on antiretroviral therapy could pose a latter risk and a greater public health concern: the emergence of resistant viruses with increased morbidity and mortality [31]. DDIs could potentially occur through different mechanisms; a) the induction or inhibition of CYP450 enzymes, b) phase II enzymes and c) cellular transporter/extrusion proteins (Bracchi et al., 2015). The route of administration of the drug shapes the nature and extent of the interaction, as it is known that intravenous injection (slamming) enhances the bioavailability of the substance, followed by insertion in the rectum through venous absorption towards the hepatic system, whereas oral intake implies extensive first pass metabolism [32]. Besides, the induction of the CYP450 metabolic pathway by the use of antiretroviral medication might lead to lower drug blood concentrations and therefore, to a lower perceived effect with the same dose. This could trigger different behaviors, such as an escalation, either on the dose or in the combination of

several substances, with even greater potential toxicity and the use of the intravenous route, to avoid first pass metabolism of oral intake [32]. The HIV treatments with greater potential for DDIs harm with recreational drugs are ritonavir, cobicistat or Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), such as efavirenz, nevirapine and etravirine [32].

Cariprazine was prescribed as an off-label treatment in these patients because, as a novel antipsychotic agent, it shows an excellent profile regarding tolerability and absence of pharmacological interactions in patients undergoing antiretroviral therapy [15]. Besides, cariprazine has proven to have anti-depressive properties, potentially due to its high affinity for and occupancy of D3 receptors [33]. This effect could be seen in the three patients. In these three clinical cases, tolerability was excellent, as none of the patients complained of side effects. Even more, cariprazine showed an improvement on impulsivity symptoms related with substance use in the three cases, though one of the patients only experimented a discrete improvement.

### Limitations and future research

The limitations of this study stems from the design, which does not allow causal explanations. The three patients in which off-label treatment with cariprazine was prescribed were carefully selected, meaning they might not be representative. Patients were specifically referred to the consultation for psychiatric reasons, which implies they were seeking for specialized help and showed great interest in improving. This study also conveyed a short period of time (approximately 4 weeks of follow-up) and there is no further data. Long-term effects of the treatment with cariprazine are yet to be elucidated. Only the risk domain of the MAP was used, as it was the only area we wanted to assess. It would have been interesting to perform the entire interview to search for specific differences between patients and domains.

For future research, it would be useful to study a larger group for a longer period. Moreover, more research would be necessary to determine complex interrelations between different variables, in order to establish risk factors for chemsex practices. It would be also useful to assess safety and tolerability of cariprazine, as well as efficacy for impulsive symptoms.

### Conclusion

Cariprazine may constitute a well-tolerated and safe therapeutic off-label tool in the treatment of patients with HIV and with chemsex practices, as a way to reduce impulsivity and risk behaviors. All patients showed an improvement in impulsive behaviors, assessed with the MAP. Therapeutic strategies for HIV patients who have chemsex should be multidisciplinary, encompassed in a program which includes specific approaches that cover all their needs. Nevertheless, further investigations are needed to determine the efficacy and utility of cariprazine in this group of patients.

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