Pharmacotherapy of Sexual Addiction

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2. The sentence "Despite their sAppendix uffering, patients rarely seek care due to shame and guilt..." was modified. Please check if the intended meaning is retained.

No, this is "Despite their suffering", not "appendix suffering"

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“recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with (1) non-human objects, (2) the suffering or humiliation of oneself or one’s partner, or (3) a prepubescent child or children or other non-consenting persons" [34, 35•].

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The references 83 to 85 are for the sentence at the end of "other treatments"

"In this latter case, a switch to another compound is required. In cases of anxiety, behavioral therapy is recommended as benzodiazepines might be associated with a higher risk of dependence in these patients [83–85]" (and no [78-80] as it is writted)

5. Please provide complete bibliographic details of this references 3, 48, and 49.

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6. References 53 and 55 based on original manuscript we received were identical. Hence, the latter was deleted and reference list and citations were adjusted. Please check if appropriate.

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Pharmacotherapy of Sexual Addiction

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Abstract

Purpose of Review

We reviewed recent data on sexual addiction and its treatment. We examined the different definitions of this disorder, related to the pathophysiological mechanisms. We addressed the pharmacological treatment of sexual addiction.

Recent Findings

Hypersexual behavior can be considered an addictive disorder. Sexual addiction is accompanied by significant psychiatric and addictive comorbidities and is responsible for life impairment. A comprehensive and efficient treatment must be proposed.

Summary

Selective serotonin reuptake inhibitors seem the first-line pharmacological treatment for sexual addiction. Naltrexone could be another therapeutic option. Psychotherapy and preferentially cognitive-behavioral therapy should be used in association with pharmacotherapy and treatments of comorbidities.

Keywords

Hypersexuality
Sexual addiction
Pharmacological treatment
SSRI
Chemsex
Compulsive sexual behavior

This article is part of the Topical Collection on *Sexual Disorders*

Introduction

Hypersexual behavior has a variety of names, numerous definitions, and can be explained by several models [1••, 2••, 3].

Over the past decades, there was a lack of consensus in the assessment of this disorder, as well as in the understanding of the pathophysiology. Despite their appendix suffering, patients rarely seek care due to shame and guilt or frequent denial associated with this disorder. Personal distress, as well as personal, professional, and family life impairments (77% of cases in a cohort of 349 men) [4], and the frequent somatic or psychiatric comorbidities encountered, make it a serious and severe illness [5, 6••, 7, 8]. Despite a prevalence of 3 to 10% in the general population, this disorder is often underdiagnosed and poorly treated. This article attempts to review the current literature on pharmacological treatments for sexual addiction. We systematically reviewed the literature, using MEDLINE/PubMed with the following keywords: "*sexual addiction*," "*compulsive sexual behavior*," "*hypersexualism disorder*," "*hypersexuality*," "*treatment*," and "*pharmacologic treatment*." All available articles in English or French were considered.

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Definitions and Diagnosis

Sexual addiction, also called hypersexuality or compulsive sexual behavior, refers to an uncontrolled frequency of sexual behavior, associated with compelling and irresistible craving, and which persists despite the subject's

experience of negative consequences and suffering, psychically or physically [9]. It may be continuous or episodic. Based on the Kinsey report, thresholds used to quantify the "excessive sexual consumption" are usually the following: 7 or more orgasms per week for at least 6 consecutive months (after the age of 15 years) [10], or more than one orgasm per day for 1 year or more [11].

De Alarcon and colleagues [12•] summarize the different approaches of DSM-5 and ICD-11 to classifying hypersexual behavior. For DSM-5, the conceptualization of hypersexual disorder is an addiction model but there is no current hypersexual disorder diagnosis, due to insufficient evidence to categorize it as addiction. For ICD-11, hypersexual behavior corresponds to an impulse control model, and is defined as compulsive sexual behavior disorder. Excessive sexual concerns, a "sexual filter" applied in interpersonal relationships, a feeling of loss of control (especially in frequency, time or financial cost) and depressive symptoms [2••] are also associated features.

The disorder can be subdivided into three clinical elements: repeated sexual fantasies, repeated sexual impulses, and repeated sexual behaviors (e.g., masturbation, problematic pornography use, sexual behavior with multiple consenting adults, cybersex, telephone sex, strip clubs, etc.) [2••, 13].

Clinically, sexual life is dissociated from the feeling of love, characterized by a feeling of permanent dissatisfaction, and preoccupation with thoughts of sex, with concentration difficulties in other daily domains [14].

Epidemiology

The prevalence of hypersexual behavior is around 2 to 6% in the general population [15–18].

The sex ratio is in favor of men, with a ratio from 2 to 3 men to 1 woman [9], with estimates up to 5:1 [2••, 16]. However, in women, the prevalence of this disorder is 3.1% in the general population [19, 20], and in the population of patients with sexual addiction, the proportion of women ranges between 3 and 40% [6••]. A recent survey of women ($n = 1174$) and men ($n = 1151$) has found that 7% of women and 10.3% of men in the USA showed distress and/or impairment due to difficulties in controlling sexual urges, feelings, and behaviors [21••]. In 2017, Rissel and colleagues [22•] reported that among 20,094 Australian participants, 1.2% of women considered themselves addicted to problematic pornography use vs. 4.4% of men.

The average age of onset is 18.7 years old [23]. However, most individuals do not engage in treatment until 37 years old [17]. In most cases, access to care is

difficult and patients seeking therapeutic assistance are often motivated either by legal problems, conjugal disorders, and professional issues or by somatic or psychiatric comorbidities [1, 24•]. Approximately 88% of patients with sexual addiction have a comorbid psychiatric disorder [25]. These are mainly mood disorders (72%), and anxiety disorders (38%) [26], a history of suicide attempts (19%) [27], personality disorders (17%) [28], or other addictive disorders (40–71%) [25–27]. Impulse control disorders (5–6%) [25] or obsessive-compulsive disorder (12–14%) [29] could be observed. In contrast, attention deficit disorder with hyperactivity (ADHD) is noted in 17–19% of cases. In men with high levels of hypersexuality or pornography use, ADHD should be systematically assessed.

Physically, these patients are at an increased risk of contracting a sexually transmitted disease such as HIV, hepatitis B and C, as well as syphilis or gonorrhea. They are also at risk for physical injuries due to repetitive sexual activity (e.g., anal and vaginal trauma or penile abrasions) [24 •].

Explanatory Models

The mechanisms of sexual addiction remain a source of debate and study [3, 30], as does its pathophysiology, and therefore its treatment. Its terminology is not consistent and may include hypersexuality, compulsive sexual behavior, sexual disorder with loss of control, or sexual addiction [15, 25, 31–33]. However, it has to be distinguished from paraphilias, which are defined as sexual disorders that are characterized by “recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with (1) non-human objects, (2) the suffering or humiliation of oneself or one’s partner, or (3) a prepubescent child or children or other non-consenting persons [34, 35•].”

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Interestingly, in a cohort of 47 hypersexuals as compared with 38 healthy controls, Engel and colleagues [36•] reported a higher prevalence of paraphilias (e.g., exhibitionism, voyeurism, masochism, sadism, fetishism, frotteurism, or transvestism: 47 vs. 3%). Men with hypersexual disorder were also more likely to report sexually coercive behavior (70 vs. 20%) and a higher rate of viewing images of child abuse at least once in their lives (81% vs. none in healthy controls). In sexual addiction, the risk of deviant sexual behavior such as voyeurism, exhibitionism, or rape remains poorly understood.

We are still accumulating knowledge about the nature of human sexual behavior. For sexual addiction, three major models have been proposed, based on the models of impulse control disorder (ICD), obsessive-compulsive disorder (OCD), or addictive disorder. These three distinct models highlight the

difficulties encountered in the diagnosis and treatment of these patients. The first model proposed by Barth and Kinder [37] is based on a compulsive-impulsive model, characterized by a lack of resistance to an impulse or a temptation to perform an act harmful to oneself and/or others. This model explains excessive sexual behavior as an inability to resist an impulse of sexual activity, as described in the DSM definition of the ICD [38].

To reinforce this hypothesis, of 204 hospitalized patients, 31% met criteria of ICD, of which 4.9% presented with excessive sexual behavior [39]. Accordingly, the ICD-11 has conceptualized hypersexual behavior as an impulse control disorder, and named it *compulsive sexual behavior disorder*, which is confusing for clinicians.

The second model [13] proposes the term compulsive sexual behavior, pointing to the parallel between OCD and sexual addiction, particularly with respect to the intrusive and irrepressible thoughts and behaviors. The association with anxious symptomatology or psychic tension associated with the intrusive thoughts that define OCD is also sometimes found in sexual addiction [40]. Two studies can support this model. Black and colleagues [27] showed that in 36 patients (28 men and 8 women) reporting sexual addiction, 42% reported repetitive and intrusive sexual fantasies, and 67% reported poor self-esteem after engaging in sexual behaviors. In addition, Raymond and colleagues [25] found in 25 patients (23 men and 2 women) suffering from sexual addiction, 83% reported a decrease in mental tension, and 70% described a sense of gratification after engaging in sexual behavior. They also note that the lifetime prevalence of compulsive sexual behavior is 5.6% in patients with obsessive-compulsive disorder, indicating a common bedrock between these two conditions [41].

The third model evoked by Orford [42] and also proposed by Potenza [43] proposes that hypersexuality be conceptualized as an addictive disorder [44]. Craving appears as an early state, followed by a repeated behavior that produces transient pleasure or relief from psychic distress, and is accompanied by a repeated failure to control the behavior and persistence in spite of negative consequences. In the Potenza study, 98% of patients reported withdrawal symptoms when decreasing sexual behaviors, 94% reported difficulty or even failure to control these behaviors, 92% reported excessive time spent on these behaviors, 94% reported excessive time to prepare or recover from behaviors, and 85% continued to have addictive activity despite negative physical or psychological consequences [43]. The high prevalence of addictive comorbidities further supports this hypothesis: alcohol and psychotropic drugs (42%), gambling (5%), work (28%), shopping (26%), and eating disorders (38%)

[45]. These comorbid disorders provide support for the same pathophysiological substratum.

Substance use in a sexual context or “chemsex” is a good illustration of the close relationship between hypersexual behavior and addictive substance disorder. The term refers to the use of specific psychoactive substances before or during planned sexual intercourse to facilitate, initiate, prolong, maintain, and intensify sexual activity and sexual performance [46••, 47]. Chemsex is being increasingly reported mostly by men who have sex with men (MSM), often in the context of group sexual activity, or sex parties. The most commonly used drugs are crystal methamphetamine, gamma-hydroxybutyric acid/gamma-butyrolactone (GHB/GBL), mephedrone, and less often synthetic cathinones, cocaine, ketamine or alkyl nitrites (poppers). Some of the participating men report injecting these drugs (colloquially referred to as “slamming”) [46••, 47, 48]. Most often there is a combination of drugs, often combined with erection dysfunction agents [49, 50]. The estimated prevalence of chemsex in MSM is hard to define, and ranges from 3 to 32% [51, 52]. For example, a recent study of 1648 MSM [49] found a prevalence of 6%. Prolonged sexual sessions with substance use may cause trauma (anal trauma, penis abrasions ...) [53, 54] and increase risk of sexually transmissible infections, particularly HIV and hepatitis C [53, 54]. Furthermore, living with HIV seems to be a risk factor for chemsex. Among men who report this practice, the prevalence of HIV is higher. In 90% of cases, the practice of slamming is carried out by patients who have already been infected with HIV before [54]. However, in those who engage in chemsex activity, post-exposure prophylaxis (PEP) was reported to occur in 14% of cases, and pre-exposure prophylaxis (PrEP) occurred in 4.5% of cases [55]. Vaux and colleagues [54] have found that, compared with the general population, chemsex users had more frequently used certain prevention strategies: HBV vaccination, PEP, or PrEP. Finally, according to Maxwell [46••], 14 to 25% of chemsex participants reported that chemsex had a negative impact on their psychosocial functioning. Few studies have looked at the prevalence of other addictive comorbidities. However, there is an association between chemsex, alcohol, and tobacco use disorder [51, 56]. For example, Sewell [52] found 12.9% of MSM with high risk of alcohol consumption. The link between sexual addiction or hypersexuality and chemsex is poorly investigated even if the comorbidity between multiple use of SPA and sexual addiction is known. For example, Antonio and colleagues [54] found those with polysubstance addiction had a significantly higher risk of a screening positive for sexual addiction (OR = 2.72, 95 CI 1.1–6.71).

Neurological Pathways and Neurotransmitters

In healthy humans, the proposed model of sexual behavior includes a cognitive component of stimulus processing, an emotional component related to sexual arousal and pleasure, a motivational component and a physiological component [57]. Brain regions intervening in these different aspects, such as the inferior and superior parietal lobules, the temporal lobe, the insula, and the frontal cortex [58••, 59] involve the mirror neuron system [60, 61].

In patients with sexual addiction, a major role of the mesolimbic dopaminergic system has been demonstrated [59]. The dorsolateral prefrontal cortex (DLPFC), the ventral striatum, the dorso-anterior cingulate cortex, and the amygdala play an important role in craving. Thus, the reward system, mediated by dopamine, is strongly implicated in the dependence cycle [62] with an initial activation of dopaminergic neurons in the ventral tegmental region projecting to the nucleus accumbens. The addictive cycle is linked to repeated exposures that increase glutaminergic projections to the prefrontal cortex, alter brain function, and create neuronal pathways of addictive behavior.

Other systems and other neurotransmitters modulate dopamine release and have a role in the sexual addiction system. This is the case for opiates and the hypothalamic-pituitary-adrenal axis that play a role upstream of the main dopaminergic system [63]. In addition, serotonin, through its action on sexual motivation, and on the hypothalamic-pituitary-gonadal axis and testosterone, is also a mediator of sexual activity and low levels of serotonin may be encountered in patients with sexual addiction [64••].

Comparing 19 subjects with sexual addiction and 19 healthy volunteers, Voon [58••] showed activation of the dorso-ventral cingular cortex, striatum, and amygdala during exposure to sexually explicit videos. Functional network connectivity between these three structures was also associated with greater desire in diseased subjects, with greater involvement of corticostriatal limbic circuits. Another study using functional MRI [65], found, as a result of sexual stimuli, greater activation in the left caudate nucleus, lower parietal lobe, dorsal anterior cingulate gyrus, bilateral thalami and DLPFC in a group of diseased subjects compared with the control group. The left caudate nucleus, the right anterior cingulate cortex, and the right DLPFC are associated with the motivational component of sexual desire. Activation of the thalamus was related to physiological responses.

Pharmacological Treatment

The first step in the pharmacological treatment of sexual addiction is to clearly define its diagnosis in its primary form. There are many neurological conditions

responsible for secondary hypersexualism, especially those associated to frontal and/or temporal dysfunctions [45, 66].

In addition, it is important to rule out a manic episode, hyperandrogenism, substance use including alcohol, cocaine, amphetamines or hallucinogens, certain anesthetics (propofol in particular), as well as dopaminergic agonist treatments of Parkinson's disease, restless legs syndrome or prolactinomas which may be associated with symptoms of sexual addiction [67••, 68].

There are few controlled studies of pharmacological treatment for sexual addiction. This literature review highlights several open-label trials and a few case reports. It appears, however, that, as in any model of addiction, pharmacological treatment must be accompanied by psychotherapeutic care [24•].

Treatment of multiple possible psychiatric comorbidities is recommended, as well as possible infectious or traumatic complications [1].

Selective Serotonin Reuptake Inhibitors

Selective Serotonin Reuptake Inhibitors (SSRIs) modulate the concentration of pre- and post-synaptic serotonin. They obviously have a place of choice in the treatment of depressive or anxious comorbidities. In addition, their side effects on sexual behavior are well known and could be directly involved in the specific treatment of sexual addiction. A 12-week double-blind study, including 28 homosexual or bisexual subjects with sexual addiction, compared the efficacy of 20–60 mg citalopram versus placebo. The results demonstrated a significant reduction in sexual desire, masturbation frequency, and use of pornography, but not in the number of partners [64••]. Moreover, the study reported the use of citalopram to treat excessive masturbation and pornographic use [69, 70].

Fluoxetine also appears to be a promising treatment for excessive sexual behavior and its anxio-depressive comorbidities. In an open-label, 12-week trial, 10 men who met the DSM III-R criteria for sexual addiction received between 20 and 40 mg of fluoxetine. Most participants (95%) met the criteria for dysthymia and 55% met criteria for a major depressive episode. After 4 weeks of treatment, a statistically significant reduction of sexual addiction was found regardless of the level of mood improvement, while there was no pharmacological effect on non-pathological sexual behavior [71]. Although less rigorous, case studies have also shown promising avenues for treatment. Elmore reported an improvement in symptomatology of sexual addiction in two patients: one treated by sertraline and one by paroxetine [72].

Nefazodone

Nefazodone is a phenylpiperazine antidepressant that selectively blocks 5-HT2A post-synaptic receptors and moderately inhibits the reuptake of serotonin and norepinephrine. In an open study, 14 patients received nefazodone (average daily dose 200 mg); 6 reported improvement and 5 patients reported a remission of obsessions and sexual compulsions [13].

Topiramate

Topiramate is an antiepileptic drug that appears to have an “anti-impulsive” effect, particularly used in the treatment of alcohol addiction, binge eating, and kleptomania. It has different operating modes including an action on the voltage-dependent channels of sodium and calcium ions, on GABA and on glutamatergic AMPA receptors. Two case reports were brought to our attention. The first, in 2005, reported the case of a 32-year-old patient, who had been treated with cognitive-behavioral therapy (12 sessions), fluoxetine (80 mg/day), and naltrexone (25 mg/day), without clinical improvement. After 6 weeks, treatment with 200 mg of topiramate resulted in a significant reduction in the frequency of sexual activity, the money spent on sexual activities, and feelings of distress. After a spontaneous cessation of the treatment, he experienced a return of his symptomatology, and following the reintroduction of the treatment, the same improvement [73]. In the second case report [74], a treatment with 50 mg of topiramate per day for 4 months led to improvement in inappropriate sexual behavior. Interestingly, the same findings were observed after the medication was termination, and then subsequently restarted.

Naltrexone

Naltrexone is an inhibitor of endogenous and exogenous opiates and blocks dopaminergic release in the nucleus accumbens, acting on the reward system. It has been shown to be effective in the treatment of alcohol and opioid addiction [75, 76]. Following studies have reported its efficacy in the treatment of sexual addiction. In monotherapy, Grant and Kim [77] reported a case of a patient with kleptomania and sexual addiction effectively treated with naltrexone. In polytherapy, several studies have shown a reduction of sexual addiction, especially after failed trials of SSRIs alone. In 2015, Kraus reported the case of a patient with sexual addiction, who was effectively treated with 50 mg per day of naltrexone monotherapy. During the 9 weeks of treatment, the intensity of his sexual urges significantly decreased and he also viewed pornography less often [78].

Raymond and colleagues [79] reported two clinical cases in which the symptoms of sexual addiction were significantly improved with a combination of naltrexone (150 mg per day) and fluoxetine (10 mg per day) in the first case, and a combination of naltrexone (100 mg) and citalopram (40 mg) in the latter case. In both cases, symptoms were significantly reduced during a follow-up period of 8 months to 1 year. Similarly, Bostwick and Bucci [80] reported the case of a patient treated with a combination of sertraline (100 mg daily) and naltrexone (50–150 mg daily). Ryback [81], in an open prospective study, investigated the efficacy of a treatment combining cognitive-behavioral therapy and naltrexone in young patients with hypersexuality and pedophilic disorders. Other treatments could be taken such as antidepressants, mood stabilizers, antipsychotics, GhRH analogs, or stimulants. The efficacy endpoint was a reduction of at least 30% in symptoms over a period of more than 4 months. In 14 of the 21 patients included, treatment was found to be significantly effective. However, 13 of them showed a resurgence of symptomatology when naltrexone was decreased below 50 mg per day. Five out of six non-responders benefited from leuprolide therapy.

Hormonal Treatments

Hormonal treatments such as antiandrogens or GnRH analogs are used in the treatment of severe paraphilias, especially those associated with a high risk of sexual assault [34]. They are not used in sexual addiction unless severe comorbid paraphilic disorders are present. In this latter case, please refer to our guidelines with a recent update in 2019 [34, 82].

Other Treatments

Baclofen is a GABAb agonist used in spastic contractures of cerebral origin. It has been shown to be effective in the treatment of withdrawal in alcohol dependence and appears promising in GHB/GBL withdrawal in addition to benzodiazepines. To our knowledge, there is no study that has investigated the efficacy of baclofen in sexual addiction.

Lithium, valproate, or antipsychotics is used in cases of psychiatric comorbidity (e.g., bipolar disorder or schizophrenia). However, it is important to keep in mind that several antipsychotics (mainly aripiprazole, but also clozapine and risperidone) have been associated with hypersexuality. In this latter case, a switch to another compound is required. In cases of anxiety, behavioral therapy is recommended as benzodiazepines might be associated with a higher risk of dependence in these patients [78–80].

Conclusion

Sexual addiction has had many names, definitions, and explanatory models, and is now considered an addictive disorder by most of the clinicians, although controversies persist. Well-designed studies conducted with large samples are lacking. SSRIs appear to be an appropriate first-line pharmacological treatment for patients with sexual addiction, but again, larger and more sophisticated studies are needed. Pharmacological treatment should be considered part of a more comprehensive care plan including psychotherapy, and in most cases, cognitive-behavioral therapy, specifically. In all cases, psychiatric and somatic comorbidities should be treated in parallel. Self-help groups adapted from the 12-step model and practice of Alcoholics Anonymous may be helpful.

Publisher's Note

Compliance with Ethical Standards

Conflict of Interest Leo Malandain, Jean-Victor Blanc, and Florian Ferreri each declare no potential conflicts of interest. Florence Thibaut is the Editor-in-Chief of Dialogues in Clinical Neuroscience. The journal receives a grant from Servier.

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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Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance

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AQ5

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