Send Orders for Reprints to reprints@benthamscience.ae

Current Drug Targets, 2018, *19*, 1391-1401

REVIEW ARTICLE

Hypersexuality As a Neuropsychiatric Disorder: The Neurobiology and Treatment Options

Muna Asiff[1,#], Hatta Sidi[1,*], Ruziana Masiran[2], Jaya Kumar[3], Srijit Das[4], Nurul Hazwani Hatta[5] and Cesar Alfonso[6]

[1]Department of Psychiatry, Faculty of Medicine, Universiti Kebangsaan Malaysia, Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; #Faculty of Medicine, Universiti Sultan Zainal Abidin, Medical Campus, 20400 Kuala Terengganu, Terengganu, Malaysia; [2]Department of Psychiatry, Universiti Putra Malaysia, Serdang, Selangor, Malaysia; [3]Department of Physiology, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; [4]Department of Anatomy, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; [5]School of Medicine, Medical University of Galway, Galway, Ireland; [6]Department of Psychiatry, Columbia University Medical Center, 262 Central Park West, Suite # 1B, New York, NY 10024, USA

ARTICLE HISTORY

Received: February 10, 2017
Revised: February 28, 2017
Accepted: March 09, 2017

DOI:
10.2174/1389450118666170321144931

Abstract: Hypersexuality refers to abnormally increased or extreme involvement in any sexual activity. It is clinically challenging, presents trans-diagnostically and there is extensive medical literature addressing the nosology, pathogenesis and neuropsychiatric aspects in this clinical syndrome. Classification includes deviant behaviours, diagnosable entities related to impulsivity, and obsessional phenomena. Some clinicians view an increase in sexual desire as 'normal' *i.e.* psychodynamic theorists consider it as ego-defensive at times alleviating unconscious anxiety rooted in intrapsychic conflicts. We highlight hypersexuality as multi-dimensional involving an increase in sexual activity that is associated with distress and functional impairment. The aetiology of hypersexuality is multi-factorial with differential diagnoses that include major psychiatric disorders (*e.g.* bipolar disorder), adverse effects of treatments (*e.g.* levodopa-treatment), substance-induced disorders (*e.g.* amphetamine substance use), neuropathological disorders (*e.g.* frontal lobe syndrome), among others. Numerous neurotransmitters are implicated in its pathogenesis, with dopamine and noradrenaline playing a crucial role in the neural reward pathways and emotionally-regulated limbic system neural circuits. The management of hypersexuality is determined by the principle of *de causa effectu evanescent,* if the causes are treated, the effect may disappear. We aim to review the role of pharmacological agents causing hypersexuality and centrally acting agents treating the associated underlying medical conditions. Bio-psycho-social determinants are pivotal in embracing the understanding and guiding management of this complex and multi-determined clinical syndrome.

Keywords: Hypersexuality, normality, neuropsychiatry, bio psychological treatment, neurobiology, libido.

1. INTRODUCTION

Hypersexuality is a subjective and wide-ranging term [1] that refers to abnormally increased or extreme involvement in any sexual activity [1, 2] or libido [3], which deviates from what is determined as average by consensus or societal standards.

A fundamental tenet of hypersexuality can be traced back to centuries when historically it was clinically viewed and classified as psychopathology and socially deviant behaviour [4-6]. Allen [7] described the term satyriasis, and Ellis [8] proposed a concept of nymphomania to denote hypersexuality among men and women, respectively. The term hypersexuality was used to describe those who exhibited an excessive preoccupation with sexual fantasy, sexual activity or masturbation [9, 10]. Epidemiological data and clinical research reveal that non-paraphilic hypersexuality consists of excessive sexual behaviours and disorders that cause personal suffering, associated with significant personal and social impairment and psychiatric morbidity [1].

*Address correspondence to this author at the Department of Psychiatry, Faculty of Medicine, Universiti Kebangsaan, Kuala Lumpur, Malaysia;
Tel: +603 – 9145 6142; Fax: +603 – 9145 6681; E-mail: hattasidi@hotmail.com

1.1. The Concept of Normality: Hypersexuality, or 'ou pas du tout'?

Normality can be viewed in many ways [11], especially when determining if a person has a psychiatric disorder, (or when we categorized people as mentally ill) or not [12]. We need to determine whether a person presents clinically with hypersexuality, or "not at all" ("ou pas du tout"). This conceptual framework of illness *vs*. normal behaviour is based on the 'normality' perspective. The concept of normality or how we distinguish normal from abnormal behaviour can be understood from numerous contexts and attributes.

Normality epitomises an aggregate of a system's main attributes. In a utopian or ideal situation normality is associated with a state of happiness [11]. Hypersexual people may be initially happy from the perspective of incentives-rewards, but later distressed by the adverse effects of excessive sexual behaviour. Normality is also based on the concept of health, which is understood as the person's bio-psycho-socially determined wellbeing [13]. This relates to the concept of "health as a sovereign pleasure" [11]. Normality can be viewed as a "process" [11]. Happiness in a utopian setting is much more

1389-4501/18 $58.00+.00

complicated than health, as it relates to *eudaimonia i.e.* welfare or *summum bonum, i.e.* "being an end in itself, and at the same time containing all other goods" [11]. Being excessively happy is not without complications [14, 15]. The concept of normality can also be viewed as average, based on the statistical concept for deriving reference limits, *i.e.* on a central metric which is often complex and inexact in medicine. The concept of reference values delineates normality without clarity [16, 17]. As reference values seem crucial to human medicine [18], this theoretical relationship links the concepts of normality and abnormal sexual behaviour (hypersexuality). Lerner *et al.* [16] postulated that the concept of normality could be separated from statistical normality (Fig. **1**).

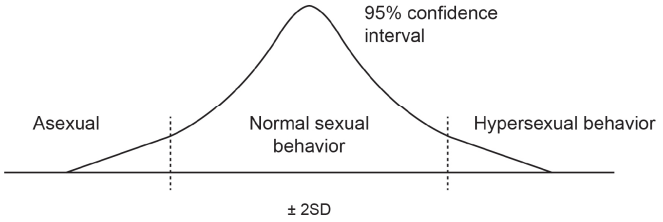

Fig. (1). Illustration of the concept of normality, based on statistical average, *i.e.* a 'normal' distribution (after Peter *et al.* [18]).

Hypersexuality is not considered a variant of paraphilias; alternatively, it is included under the unspecified sexual disorders in the current Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [19], since as an entity it lacks research validation as a distinct diagnosis [20]. Kafka [9, 21] viewed hypersexuality as a non-paraphiliac sexual disorder with a strong association with obsessional phenomena. The description of this condition as sexual obsessive-compulsivity was shared by many clinicians and researchers [2, 22-25], despite some disagreement [26, 27]. The term hypersexuality was introduced to illustrate extreme and disproportionate sexual behaviour associated with a person's inability to control his or her sexual actions [2]. This medical syndrome is frequently associated with sexual disinhibition in the form of inappropriate or indecent sexual behaviour that causes distress [3, 28]. Adverse effects on the community, *i.e.* crime rates [29], psychological and personality dysfunction [30], marital complications [31] and other high risk behaviours [32-34] were recognized as complications of hypersexuality.

Different perspectives were used to describe the occurrence of persistent high frequency sexual behaviour that is considered abnormal for an individual. There is a debate to think of hypersexuality as impulsivity or impulse control disorder or as a compulsive disorder [9, 10]. Few clinicians consider it an addiction disorder [35-38], while others see it as an obsessive-compulsive compulsive disorder (OCD) or in the OCD spectrum. Interestingly, a number of researchers do not perceive such behaviour as pathology and instead assert that hypersexuality simply reflects a cultural dislike of incomparable sexual conducts [39, 40]. Few have questioned whether hypersexuality is just a problem with high sexual desire rather than a more complex psychopathological state [27], or whether it is an ego-defense mechanism that occurs in an adaptive attempt to alleviate anxiety [26]. From a psychodynamic perspective, the hypersexuality-obsessional prism is viewed as affective ambivalence, *i.e.* formed by the love/sex split, denial, idealization and omnipotence [26]. Despite controversy and lack of consensus on the definition of hypersexuality, a central feature of this clinical syndrome is excessive sexual behaviour in a person.

Consistent with lack of agreement and weak diagnostic validity over how to conceptualize hypersexuality [9], researchers and clinicians have used diverse terminology interchangeably and with bias. Terms used include compulsive masturbation, obsessive-compulsive sexual behaviour [35, 41], cyberponography [42-48], de Clérambault's syndrome (or erotomania) [49, 50], and out of control sexual behaviour [51]. In youth, hypersexuality may be associated with psychiatric illness and with numerous socio-demographic risk factors such a dysfunctional family unit and societal stress [52, 53]. According to Kafka and Hennan [54], hypersexuality in the general population is estimated to occur in 1/15 individuals, with a mean age around 19 years and average duration of 12 years. Surveys have found male preponderance with a male to female ratio of 5 to 1 [55]. We caution readers to consider these statistics as inexact since a uniform definition is not available and there could be subjective bias.

At present research on hypersexuality is in its infancy due to difficulty measuring the condition objectively and lack of an operationalized diagnostic framework and definition [56]. Nevertheless, as we develop a more careful understanding of its neurobiology and psychosocial determinants, a diagnosis within the context of this clinical entity could soon be accepted in its future classification as a neuropsychiatric disorder or syndrome [20, 21, 57, 58]. As we cannot be oblivious of the importance of managing hypersexuality because of morbidity to patients and consequences to society, we feel it is important to highlight its clinical importance for scientific discussion. This step is pivotal especially as the wide-use the Internet exponentially increases leading to hypersexuality with cyberponography as complicating issue [42-48].

In this review, we highlight a dimensional theoretical perspective of hypersexuality, based on the tenet concepts of distress, impairment of functioning and severity of the hypersexual psychopathology [1, 9, 21]. Fig. (**2**) depicts hypersexuality as multi-dimensional with multi-determined psychological attributes.

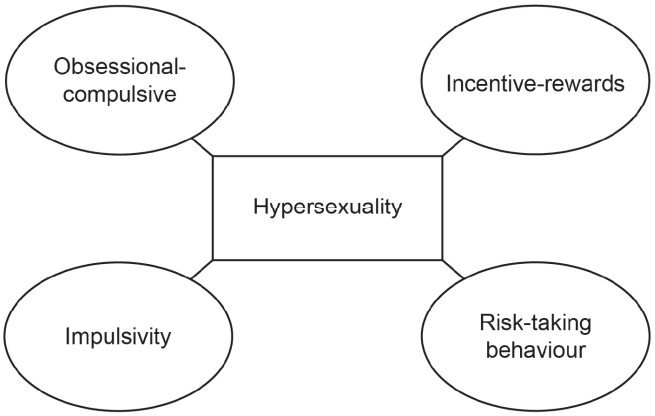

Fig. (2). The tenets of hypersexuality.

In Fig. (**3**) a model of hypersexuality is conceptualized as sexual content psychopathology, which is associated with sexual behaviour that is excessive [2] or intense normophilic sexual thoughts, urges and behaviours [30] that may be inappropriate at times. The psychopathology and behaviour are weighted between feelings of being rewarded *vs*. taking risks, which may have negative consequences for the affected person. It causes distressing emotions in the individual as well as to others around him or her [3, 28].

Hypersexuality may be regarded as a proviso, or as a manifestation of other secondary conditions, such as psychopathology, a psychiatric illness, or medical condition, as a secondary diagnosis. For example, hypersexuality is a recognized psychopathological manifestation of Klüver-Bucy syndrome [3, 59], or mania or hypomania in bipolar disorder [60-62], or as adverse effects of dopamine agonist treatments for Parkinson's disease. Hormonal treatments such as testosterone, estrogens and other sex hormones may also be implicated in hypersexuality [63-65]. Some of the potential causes of hypersexuality were illustrated in Fig. (**4**).

2. DIFFERENTIAL DIAGNOSIS OF HYPERSEXUALITY IN NEUROPSYCHIATRY

Hypersexuality is associated with mood disorder comorbidity in up to 72% of cases as reported by Kafka and Hennan [54]. Interestingly, even though reduced libido is part of the symptomatic presentation of depression, paradoxical hypersexuality has been observed in some patients with pre-existing depression [66]. Another prevalent comorbidity associated with hypersexuality is substance abuse, in up to 71% of cases as reported by Raymond and colleagues [67] and 64% by Black and colleagues [68]. In a study published in 2015, 79% of respondents with hypersexuality self-report use alcohol recreationally [69]. Individuals using centrally acting stimulants such as ampethamines, and opioids like heroin are more likely to be involved in high-risk sexual behaviours [70]. Approximately 17% of patients with hypersexuality have co-morbid personality disorders [71] and 15% have co-morbid obsessive-compulsive disorders [67].

3. BIPOLAR DISORDER WITH HYPOMANIC/MANIC EPISODES

The psychopathology of mania with associated hypersexuality results from increased dopaminergic activity [72]. Agents that increase dopamine will elevate mood in vulnerable patients, whereas drugs which reduce dopamine in central nervous system (CNS) ameliorate mania. Drugs that enhance dopaminergic neurotransmission include agents that increase synthesis of dopamine (levodopa), drugs that encourage dopamine release (amphetamines), and drugs that operate directly as dopamine agonists (bromocriptine). All of these have been reported to precipitate mania [72]. Conversely, drugs that reduce dopamine activity by inhibiting its synthesis, (α-methylparatyrosine) or by inhibiting the dopamine receptors (pimozide) are effective in reducing manic psychopathology. Dopaminergic activity does not occur in isolation as there is evidence of central cholinergic and GABA-ergic processes modulating mania or manic symptoms. There is interplay of neurotransmitter neural pathways connecting the limbic organization and the ventral tegmental area, VTA (A10) region involving dopamine, acetylcholine and GABA that relate to the course and prognosis of manic illnesses.

4. NEUROPSYCHIATRIC DISORDER

Neuropathology in the form of a lesion in the amygdala, epilepsy, head trauma, and parkinsonism are associated with hypersexuality, including hypersexuality due to L-Dopa treatment, frontal lobe syndrome, and disinhibition seen in Alzheimer's disease. Hypersexuality is observed in patients

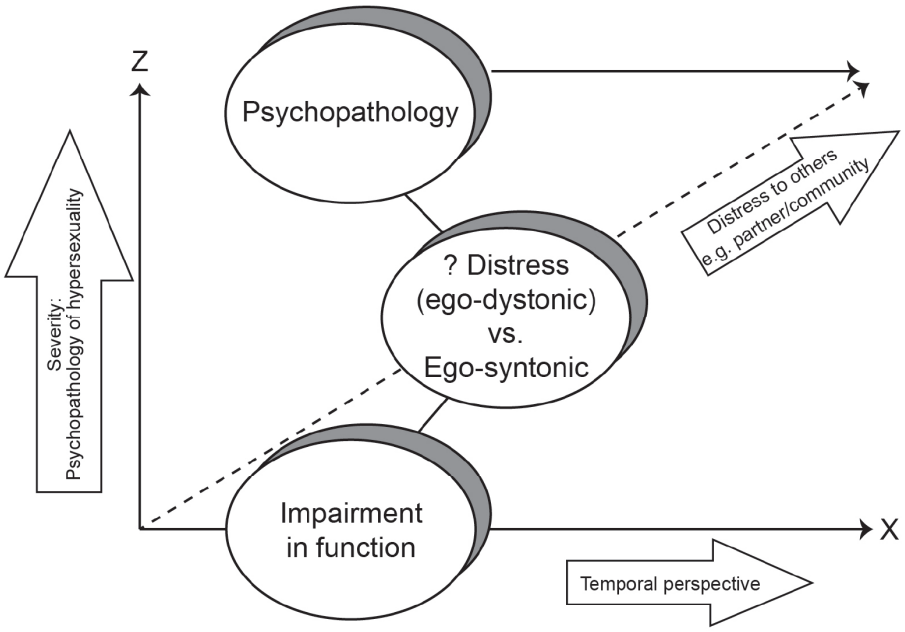

Fig. (3). The conceptual framework of hypersexuality from the perspective of psychopathology, distress level and impairment of self-occupational-social functioning [1, 9, 21].

given anti-parkinsonian agents, suggesting that the inhibition of prolactin through dopamine agonists may increase libido [73]. Sexuality is among the many functional areas affected by traumatic brain injury (TBI). Hypersexuality, particularly inappropriate sexual remarks and gestures, is a recognized result of TBI [74]. Neuropathological disorders like dementia, Parkinson's disease, HIV associated neurocognitive disorders, Huntington's Disease, subcortical dementias and other neuropsychiatric problems like vascular dementia [75] may also be associated with hypersexuality. Hypersexuality is a common presentation in cognitively impaired geriatric patients [75, 76]. Frontal lobe lesions or damage may present with sexual disinhibition, which could partially explain increased sexual activity and decreased control by the prefrontal region [77].

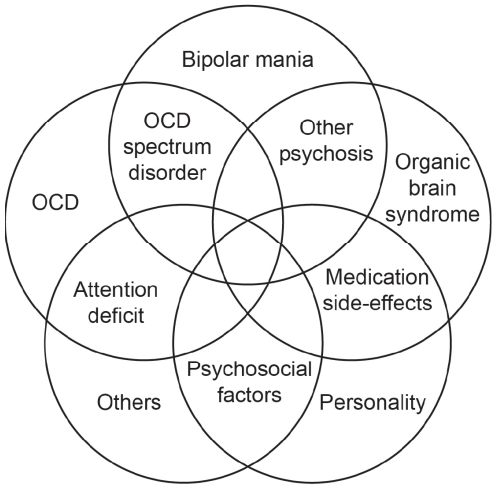

Fig. (4). The differential diagnosis of hypersexuality as a clinical syndrome.

5. PERSONALITY TRAITS AND DISORDERS AND EARLY CHILDHOOD ADVERSE EVENTS

Hypersexuality is usually not associated with personality disorders with the exception of borderline and narcissistic personality disorders [78, 79]. Nevertheless, psychological traits like insecurity, impulsiveness, low ability to tolerate frustration, and problems coping with intense emotions are personality factors that correlate with hypersexuality [80]. From a psychodynamic perspective, those with disconnected families and insecure attachment styles, childhood emotional abuse and early exposure to pornography or inappropriately witnessing adult sexuality may develop sexual compulsions and hypersexuality in adulthood [81]. Bergner [82] suggested that at the core of sexual compulsion was an effort to recover from adverse childhood experiences. Sexual trauma is associated with risky sexual behaviours in adulthood. Personality traits and family background are also elements that compound treatment challenges, as the persons with hypersexuality and sex addictions have difficulty trusting, lack in confidence in intimacy and resist collaborative relationships [83]. Post-traumatic stress disorder (PTSD) from early childhood sexual trauma needs to be considered as a possible antecedent of adult hypersexuality, since it has been demonstrated to correlate with risky sexual behaviors in adulthood [84].

Persons with hypersexuality and comorbid personality disorders use sex to reduce their level of distress, anxiety and increase their self-esteem unconsciously displacing internal conflicts [85]. Raviv [86] supports the notion that sexual addiction can be explained as a means of coping with interpersonal difficulties.

6. THE NEUROBIOLOGY OF SEXUAL BEHAVIOUR AND HYPERSEXUALITY

Sexual desire that leads to hypersexuality is the culmination of different neural mechanisms in various areas of the CNS activating at different times the sexual response cycle [87-90]. Sexual drive is also regulated by internal biological determinants such as hormone levels, neurotransmitters and psychosocial factors such as the sexually related triggers, which are further regulated *via* cognitive processing of the inter-play of factors that produce variations in sexual arousability. Enhanced risk-taking behaviour in the form of hypersexuality may be motivated by increased brain incentive-reward processing, or by reduced sensitivity to negative sequelae [91]. There is feedback reinforcement in the incentive-reward pathway, where the ultimate goal in hypersexuality is to engage in sexual risks [92].

Sexual drive and sexual risk-taking mirror constant oscillations in sexual arousal, incentives and neural inhibition. Winters and colleagues [27] observed sexual regulation difficulties in those reporting higher levels of the sexual drive. Sexual desire is the pinnacle of numerous distinctive neural mechanisms; each is regulated in different areas within the CNS and is galvanized at different times during the sexual response cycle. The sexual response cycle contribution to hypersexuality is two-pronged, as sexual desire may need to be down regulated to avoid problematic sexual behaviour or up regulated to reinforce romantic/sexual relationship functioning.

7. NEUROCHEMICAL INTERPLAY MEDIATING SEXUAL FUNCTION

In addition to dopamine, another important brain chemical, *i.e*. noradrenaline, co-steers the brain pleasure circuitry [93]. Serotonin, in addition, has modulatory effects on both dopamine and noradrenergic systems [94]. Serotonin is found in the gastrointestinal tract, CNS and platelets [95, 96]. Serotonergic neurons project from the raphe nuclei in the midbrain and connect to the diencephalons, including hypothalamus, limbic and cortical regions, hippocampus and spinal cord to the lower lumbar and sacral regions (S2 – S4) that control genital reflexes [95, 96]. Meyerson [97] states that the serotonergic system is linked to sexual inhibition, and dopamine and serotonin neural organization are interrelated and synergistically inhibit sexual behaviour. Pharmacological agents that inhibit serotonin synthesis or free receptor binding increase sexual behaviour. An experiment directly infusing serotonin to the hypothalamus or to the nucleus accumbens area of male rats resulted in delayed ejaculation in the rodents [98]. Interestingly, sexual desire and behaviour are linked with earlier and/or later experiences of sexual gratification, which are encoded in the hippocampus, the memory consolidative area and the neocortex, especially the prefrontal region influenced by dopamine [94]. The do-

paminergic pathways originating from the VTA to the nucleus accumbens show stimulation during orgasm in men and women in studies involving monitoring of brain activity [99-101]. There is also observed activation of the cerebellum and the anterior cingulate gyrus [99, 101, 102]. Stimulation of the frontal cortex shows increased activity during orgasm in women only [100]. Serotonin blocking reduces the function of dopamine and noradrenaline, which is beneficial for sexual arousal and orgasm to occur [94-96]. For sexual arousal, prolactin has a negative effect, where for orgasm, oxytocin has a positive role [94-96].

8. LIMBIC SYSTEM: THE PLEASURE CENTRE

The limbic region is the headquarter of pleasure producing circuitry. It is composed of interrelated structures such as cingulate gyrus, hippocampus, hypothalamus, thalamic nuclei and amygdala. The limbic centre contains dopaminergic pleasure activation from the nucleus accumbens (NAc), a region within the ventral striatum that mandates rewarding behaviours, including sexual [1]. NAc receives dopaminergic input, predominantly from the ventral tegmental area (VTA), where the dopaminergic neural cell bodies of the mesolimbic and corticolimbic dopamine system originate, and the axon terminals of the dopaminergic projection reside in the NAc. Stimulation of VTA either by drugs or euphoric stimuli results in a dopamine-driven pleasure rush in the NAc that create hedonistic sensations [103, 104]. Besides the NAc, the dopaminergic projections from VTA release dopamine to other brain regions in the limbic system such as amygdala, hippocampus, striatum, and the prefrontal cortex, which collectively create pleasure memories that are strongly associated with accompanying reinforcing emotions [105]. Other limbic associated structures such as the striatum play a vital role in execution of motor control, reinforcement (learning), perceptual assessment and decision making [106]. The dopaminergic projections from VTA along with another region known as substantia nigra pars compacta regulate important cognitive functions such as motivation, reward associations and habit learning [107] that are instrumental in repetition of rewarding activities. Dysfunctions in the mesolimbic dopamine neuronal circuitry have been implicated in several neuropsychiatric disorders, including addiction [107] and also hypersexuality.

9. THE ROLE OF CORTICOSTRIATAL LIMBIC CIRCUITRY IN SEXUAL BEHAVIOUR COMPULSION (SBC)

A study examining cue-reactivity fMRI tasks exposed to sexually explicit cues in individuals having SBC compared to non-SBC found different patterns of brain activation in the areas of the dorsal anterior cingulate, striatum and amygdala [92] (See Figs. **5** & **6**). The corticostriatal limbic circuitry (Fig. **5**) in SBC has a higher level of engagement and the dorsal anterior cingulate cortex (dACC)-ventral striatal-amygdala network is strongly linked to sexual desire in the SBC group [107]. Respondents with SBC subjectively report higher levels of "wanting" but not of "liking" when reacting to the video used in the study. This dissociation between "wanting" and "liking" has been hypothesized to occur once behaviour becomes an addiction. The neuroimaging evidence highlighting reward pathways as well as amygdala involvement in sexual desire and potentially hypersexuality could be taken into consideration when planning bio-psycho-social interventions for hypersexuality.

10. THE ROLE OF MEDIAL PREFRONTAL CORTEX (mPFC): THE "THINKING" BRAIN

The medial prefrontal cortex (mPFC) is implicated in numerous higher mental functions of the CNS, including regulation of the basic emotional drives, *i.e.* mood, anxiety and fear-like behaviours, as well as accommodative behaviour and executive function (decision making) [109-113]. The reward pathway that incorporates decision making is regulated by the region of the neo-cortex and sub-cortical inner circuit of the mPFC, amygdala, and striatum, where the mPFC acts as a higher mental neuroregulator of this 'top-down' process [88-90]. The essential characteristic of reward-based decision making is the capability to temporally trail "response-outcome" relationship [87]. From this perspective, when a consequential associated behavioural activity becomes unfavourable, the frequencies of the corresponding actions diminish. This positive behavioural adaptation and response is dependent on intact mPFC function [88-90, 114]. An inability to alter behavioural actions once they lead to adverse consequences characterizes a variety of addictive disorders [115-118].

Davis and colleagues [119] researched whether the mPFC is involved in the inhibition of sexual behaviour if associated with aversive consequences. In a meticulously designed study with rats, the researchers found that lesions of the mPFC result in compulsive sexual behaviour. In contrast, lesions did not alter sexual function or the learning associated with reward or aversive stimuli. The findings support the viewpoint that the mPFC exerts control on behavioural inhibition once the behaviour is connected with aversive outcomes [119]. Sexual compulsive behaviour has a high association of co-morbidity with psychiatric disorders, including substance abuse and mood disorders. Davis and colleagues study [117] suggests that mPFC dysfunction may contribute to sexual risk-taking or to compulsive sexual behaviours. Although thought-stimulating, we do not yet know whether these findings can be generalized to humans [119].

11. THE ROLE OF AMYGDALA IN HYPERSEXUALITY

The amygdaloid complex located in the medial aspect of temporal lobe, is an anatomically diverse structure that comprises 13 nuclei, which play crucial roles in modulation of emotion [120] and sexuality [121]. The three major efferent pathways projecting from the amygdala are the stria terminalis, amygdalofugal and the anterior commissure pathways [122]. The amygdalofugal pathway linkes the corticomedian nuclei of the amygdala with the diencephalons (*i.e.* thalamus and median hypothalamus), brain stem and nucleus accumbens. This nerve pathway is thought to modulate pleasurable feelings. The stria terminalis has neural projections to and from the hypthothalamic-pituitary-adrenal (HPA), believed to modulate threat monitoring and the stress diathesis. It is thought to be instrumental in activating the autonomic nervous system. The anterior commissure links the left and right amygdala.

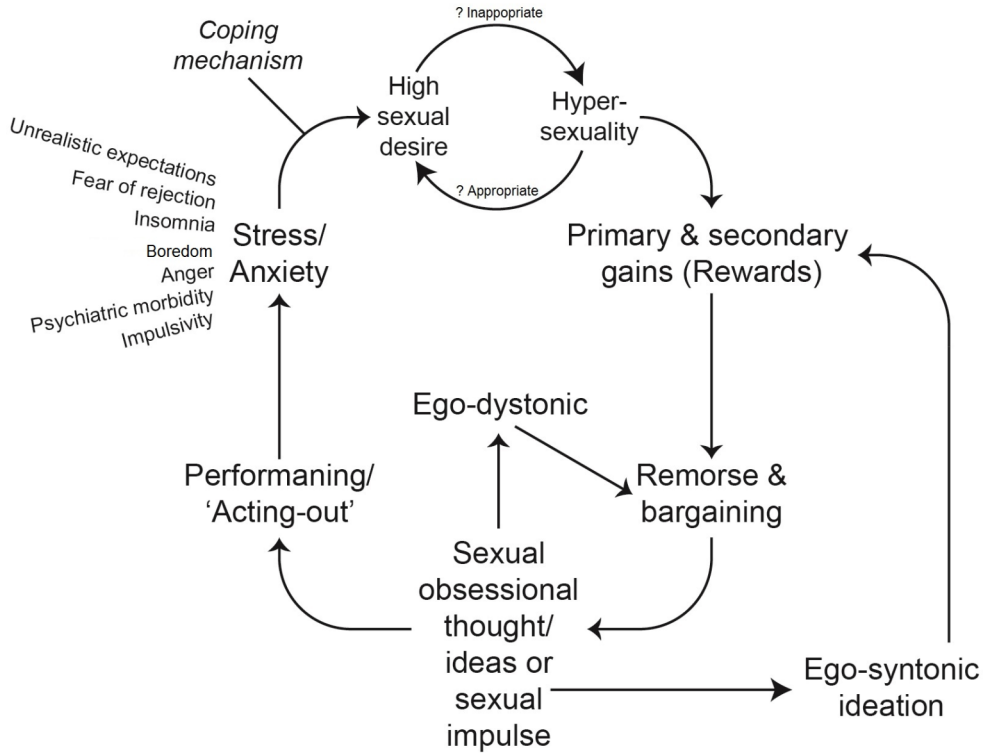

Fig. (5). Neurobiological correlates of psychological aspects of hypersexuality.

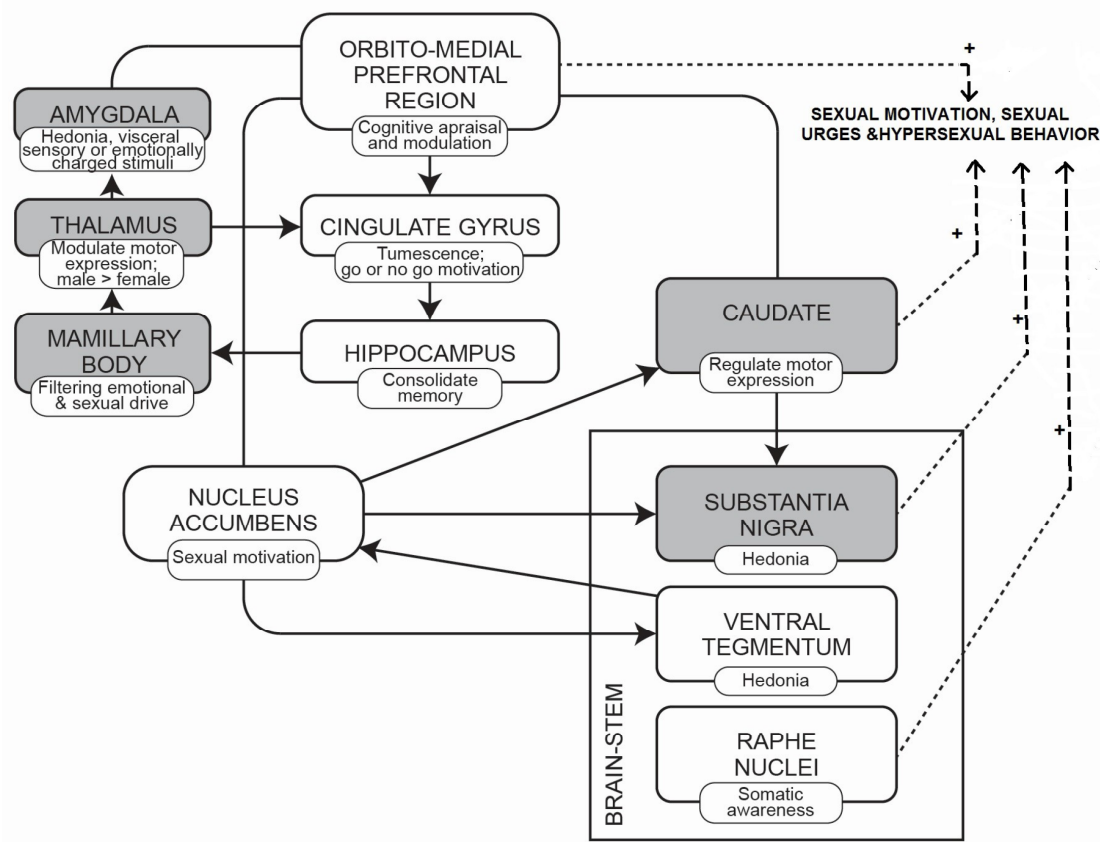

Fig. (6). The neurobiological pathways of hypersexuality [108].

Activation of the amygdala through the limbic system may trigger arousal, sexual feelings and orgasm [87-90]. A study by Everitt and colleagues in 1989 [121] showed that the basolateral region of the amygdala may interact with the ventral striatum in a dopamine dependent manner in stimulus-reward associations of sexual reinforcement. This finding

was preceded by another study where Masco and Carrer using female rats to demonstrate that the amygdala may play a modulator and integrative role for the control of sexual behaviour [123]. In humans, more recent studies have directly examined the role of the amygdala in sexual functioning [124]. Researchers compared the amygdala volumes of patients associated with or without sexual behaviour alterations following temporal lobe resection for epileptic fits and age-matched controls. The study reported that larger contralateral amygdala volume may lead to increase or improved sexual function after temporal lobe resection [124]. The role of amygdala in mediating sexual function has also been considered in a series of functional neuroimaging studies [125, 126].

Kluver-Bucy syndrome results in pathological hypersexuality caused by bilateral lesions of the medial temporal lobe and uncus together with the amygdaloid nucleus [127]. Heightened sexuality is the characteristic behaviour of the syndrome as a result of bitemporal damage [123, 128]. Amygdala induced hypersexuality may be mediated by how it regulates emotional response. It is known that the amygdala influences the attachment of appropriate emotional relevance to sensory input, reinforcing or helping discriminate the nature of the stimuli [129]. It is hypothesized that the amygdala helps process emotional stimuli better, especially social or sexual cues and also the attachment of significance to the related stimuli, with implications on sexual response and hypersexuality [130].

12. THE ROLE OF PHARMACOLOGICAL AGENTS IN HYPERSEXUALITY

12.1. Antidepressant, Antipsychotic and Mood Stabilizers

Decreased serotonin and increased dopamine levels are found in patients with hypersexuality [131]. Patients who are on SSRIs are subjected to excessive serotonergic effects in the CNS resulting in lower sexual desire as well as impairment in other domains of sexual functioning. Hypersexuality is recognized in a number of patients taking anti-parkinsonian treatment, suggesting that the inhibition of prolactin through dopamine replacement may contribute to increased libido [73].

Based on how they modulate neurotransmission, the use of serotonin reuptake inhibitors (SSRIs) and dopamine blockers have been recommended as psychopharmological agents in the treatment of hypersexuality (Fig. **7**). The use of SSRIs like citalopram has been shown to be effective in reducing sexual drive, masturbation, and watching pornography in men with compulsive sexual behavior [132]. Fluoxetine has been shown to lessen hypersexuality in men as well [133]. Case reports describe how the use of typical antipsychotics, *e.g.* haloperidol, or atypical antipsychotics, *e.g.* risperidone and quetiapine, in elderly hypersexual patients with dementia may be effective to curb hypersexuality [134].

Clomipramine, which is a type of tricyclic antidepressant, has shown efficacy in the treatment of obsessive-compulsive disorder (OCD). As paraphilias and OCD have some similarities, clomipramine has been given to patients with paraphilias [23, 135, 136]. In one report clomipramine 150 mg daily reduced sexual urges and fantasies in patients with exhibitionism [137-139].

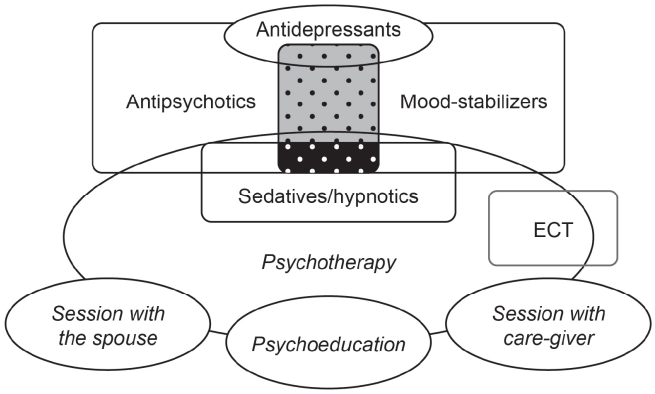

Fig. (7). Psychopharmacology and psychological interventions in the treatment of hypersexuality.

An early study by Coleman [140] on 13 patients with paraphilias reports a decline of paraphilic behaviour in patients receiving lithium and lithium plus fluoxetine. The doses of lithium were in the range of 600-1800 mg/ day and only caused minimal side effects. These treatments were successful, particularly in patients with paraphilias with co-morbid mood disorder. Another type of mood stabilizer, valproic acid, shows promising results in the treatment of patients with bipolar mood disorder with co-morbid sexual compulsions [141, 142].

12.2. Hormonal Treatments

Antiandrogens and gonadotropin-releasing hormone (GnRH) analogues are the agents we will discuss in this category. Antiandrogens significantly reduce testosterone levels, which results in impairment of sexual functioning and diminished hypersexual behaviour. Medroxyprogesterone acetate (MPA), leuprolide acetate and cyproterone acetate are the most frequently used antiandrogenic agents [143].

The usefulness of hormonal agents for the treatment of hypersexuality has been recognized for decades as these interventions generally exert their effects by inhibiting the synthesis of luteinizing hormone (LH) in the anterior pituitary gland, which subsequently inhibits or prevents the release of testosterone. Decreased testosterone levels contribute to reduction or elimination of sexual desire and arousal. One such treatment is triptorelin, a gonadotropin releasing hormone (GnRH) agonist acting *via* the inhibition of steroidogenesis both in the ovaries and the testes. A decrease in LH and follicular stimulating hormone (FSH) further reduces testosterone and estrogen levels. Rösler & Witztum [144] reported that 30 men treated with 3.75 mg of triptorelin for 8 to 42 months had a considerable decrease in hypersexual fantasies and while subjected to the therapy, with these effects noted after 3 to 10 months of the intervention. There are case reports and studies showing evidence about the successful role of MPA in the treatment of sex offenders [145, 146] and in hypersexual patients with dementia [147]. Leuprolide acetate as a depot also showes a notable suppression of hypersexual interests and behaviour and is considerably well tolerated [148]. Another author found beneficial effects of triptorelin with persistent reduction in LH and FSH concentration as well as reduced hypersexuality on patients treated for 24 months [28].

Another class of pharmacological agents shown to be effective in reducing the intensity and the frequency of hypersexuality are antiandrogen medications. These include cyproterone acetate (CPA) and medroxyprogesterone acetate (MPA) [149]. CPA binds androgen receptors and consequently block testosterone uptake. MPA as a progesterone agent produces a negative feedback on the hypothalamic-pituitary (HPA) axis resulting in speeding up testosterone metabolism and clearance. It also acts by binding on androgen receptors. Medroxyprogesterone has been tested in the treatment of sexual offenders in more than 600 cases. These include 12 case reports and 13 open-label studies, as well as three double-blind, cross-over studies comparing medroxyprogesterone to placebo [150].

Another hormonal intervention to be considered for hypersexuality is the use of GnRH analogues, which function as GnRH receptor agonists in the anterior pituitary. This treatment initially causes a transient increase of testosterone *via* transitory intensification of release of LH (luteinizing hormone). This occurrence is referred to as a 'flare-up'. GnRH analogues administered intramuscularly result in the rapid desensitization of GnRH receptors and decrease of LH (and gradually some reduction of FSH) and testosterone to low levels within two to four weeks [151, 152].

One type of GnRH analogue that has been used is triptorelin, showing a positive response when studied in an open-label prospective cohort on 41 men [144], one retrospective study in 31 women [153] and an open-label study comparing it with other different GnRH analogues cyproterone (29 males each experimental group) [154]. In another study a dose of triptoreline 3.75 mg administered i.m. once a month was effective on 5 out of 6 aggressive patients with hypersexuality [155].

12.3. Opioid Antagonists

A small number of studies found that the use of an opioid antagonist, naltrexone, is effective in the treatment of sexual compulsions. A case report by Grant and Kim [156] describes a case of patient with kleptomania and compulsive sexual behaviours who was successfully treated with naltrexone after failing to respond to SSRIs and psychotherapy. It is hypothesized that decreasing cravings and urges by blocking the euphoria neural pathways, as in populations with substance abuse and pathological gambling, may also help curb hypersexuality.

13. FUTURE DIRECTIONS AND CONCLUSIONS: A BIO-PSYCHO-SOCIAL TREATMENT PARADIGM

Hypersexuality is a challenging concept, and as a clinical syndrome for many researchers, embracing the concept can be demanding not only because it is not recognized as a distinctive and valid diagnosis but also because it is seen in typical and atypical situations (*e.g.* paradoxical states). It has a wide-range of etiologies, can be iatrogenic, associated with complex differential diagnoses, and approached pharmacologically or psychotherapeutically. This review highlights an important clinical area in the care of psychiatric patients with hypersexuality, but yet questions remain in relation to diagnostic agreement, management issues, and how helpful could pharmacotherapy be with or without combined psychotherapy. Optimizing management of hypersexuality could start by delineating causative factors and identifying if there is psychiatric co-morbidity, neuropathological diseases, and personality factors or disorders affecting the condition. Sessions with the patient's spouse or partner could be relevant as in the case of helping a hypersexual person with dementia in relieving the burden of care from caregivers. Psycho education on the phenomenology and pathogenesis of hypersexuality in joint sessions with the patient and caregivers can clarify and provide relief. This applies when hypersexuality is iatrogenic, results from brain injury, or is due to a co-morbid psychiatric disorder.

CONCLUSION

There is currently no clear roadmap for the bio-psycho-social investigation and treatment of hypersexuality. As researchers and clinicians in the field develop increased awareness and improved knowledge of the neurobiology and psychopharmacological understanding of this multidimensional syndrome, the bio-psycho-social paradigm provides a proper framework for study and interventions. Treatment strategies for hypersexuality currently include psychoeducation for patients, significant others and caregivers, encouraging early recognition and interventions, and providing psychotherapy in selected cases. We recommend adopting a multi-dimensional approach for the diagnosis and management, targeting the individual, his or her relatives or companion, and societal levels to deal with and improve clinical knowledge and practices. The process of making treatment recommendations for the management of hypersexuality needs to take into account that the patients symptom profile merits a multi-disciplinary effort and follow the principle of *de causa effectu evanescent.*

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors acknowledge the financial support by UKM (DIP-2014-2009).

REFERENCES

[1] Blum K, Badgaiyan RD, Gold MS. Hypersexuality Addiction and Withdrawal: Phenomenology, Neurogenetics and Epigenetics. Cureus 2015; 7: e348.
[2] Rettenberger M, Klein V, Briken P. The relationship between hypersexual behavior, sexual excitation, sexual inhibition, and personality traits. Arch Sex Behav 2016; 45: 219-33.
[3] Ibrahim C, Reynaert C. Hypersexuality in neurocognitive disorders in elderly people - a comprehensive review of the literature and case study. Psychiatr Danub 2014; 26: 36-40.
[4] disorders ACLOUPAtop.
[5] Rush B. Medical Inquiries and Observations upon the Disease of the Mind. Birmingham AL: Gryphon Editions Ltd; (Original work published 1812) reviewed in 1979.
[6] von Krafft-Ebing R. Psychopathia Sexualis. New York: Stein and Day; (original work published 1886) reviewed in 1965.
[7] Allen CA. A textbook of psychosexual disorders. London: Oxford University Press; 1962.

[8] Ellis A, Sagarin E. Nymphomania: A study of the oversexed woman New York: Gilbert Press; 1964.
[9] Kafka MP. Hypersexual Disorder: A proposed diagnosis for DSM-V. Arch Sex Behav 2010; 39(2): 377-400..
[10] Reid RC, Carpenter BN, Hook JN, *et al.* Report of findings in a DSM-5 Field Trial for Hypersexual Disorder. J Sex Med 2012; 9: 2868-77.
[11] Withington P. Utopia, health, and happiness. Lancet 2016; 387: 2084-85.
[12] Sabshin M. Psychiatric perspectives on normality. Arch Gen Psychiatry 1967; 17: 258-64.
[13] Organization WH. Constitution of the World Health Organization – Basic Documents. 45th edOtober 2006.
[14] Bentall RP. A proposal to classify happiness as a psychiatric disorder. J Med Ethics 1992; 18: 94-8.
[15] Greaves D. The obsessive pursuit of health and happiness. BMJ 2000; 321: 1576.
[16] Lerner H, Berzell M. Reference values and the problem of health as normality: a veterinary attempt in the light of a one health approach. Infect Ecol Epidemiol 2014; 4.
[17] Siest G, Henny J, Gräsbeck R, *et al.* The theory of reference values: an unfinished symphony. Clin Chem Lab Med 2013; 51: 47-64.
[18] Pater C. The Blood Pressure "Uncertainty Range" – a pragmatic approach to overcome current diagnostic uncertainties (II). Curr Control Trials Cardiovasc Med 2005; 6: 5.
[19] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: Author; 2013.
[20] Reid RC, Kafka MP. Controversies About Hypersexual Disorder and the DSM-5. Curr Sex Health Rep 2014; 6: 259.
[21] Kafka MP. What happened to hypersexual disorder? Arch Sex Behav 2014; 43.
[22] Barth RJ, Kinder BN. The mislabeling of sexual impulsivity. J Sex Marital Ther 1987; 13: 15-23.
[23] Coleman E. Sexual compulsivity: Definition, etiology, and treatment considerations. J Chem Dependency Treatment 1987; 1: 189-204.
[24] Garcia FD, Thibaut F. Sexual addictions. Am J Drug Alcohol Abuse 2010; 36: 254-60.
[25] Stein DJ. Classifying hypersexual disorders: compulsive, impulsive, and addictive models. Psychiatr Clin North Am 2008; 31: 587-91.
[26] Estellon V, Mouras H. Sexual addiction: insights from psychoanalysis and functional neuroimaging. Socioaffect Neurosci Psychol 2012; 2: 11814.
[27] Winters J, Christoff K, Gorzalka BB. Dysregulated sexuality and high sexual desire: distinct constructs? Arch Sex Behav 2010; 39.
[28] Safarinejad MR. Treatment of nonparaphilic hypersexuality in men with a long-acting analog of gonadotropin-releasing hormone. J Sex Med 2009; 6: 1151-64.
[29] Klein V, Schmidt AF, Turner D, Briken P. Are sex drive and hypersexuality associated with pedophilic interest and child sexual abuse in a male community sample? PLoS One 2015; 10: e0129730.
[30] Kingston DA, Graham FJ, Knight RA. Relations between self-reported adverse events in childhood and hypersexuality in adult male sexual offenders. Arch Sex Behav 2016.
[31] Štulhofer A, Bergeron S, Jurin T. Is high sexual desire a risk for women's relationship and sexual well-being? J Sex Res 2016; 53: 882-91.
[32] Goodman JD. The behavior of hypersexual delinquent girls. Am J Psychiatry 1976; 133: 662-8.
[33] Sanfey AG, Chang LJ. Multiple systems in decision making. Ann NY Acad Sci 2008; 1128: 53-62.
[34] St Onge JR, Chiu YC, Floresco SB. Differential effects of dopaminergic manipulations on risky choice. Psychopharmacology (Berl) 2010; 211: 209-21.
[35] Coleman E. The obsessive–compulsive model for describing compulsive sexual behavior. Am J Preventive Psychiatry Neurol 1990; 2: 9-14.
[36] Miller BL, Cummings JL, McIntyre H. Hypersexuality and altered sexual preferences following brain injury. J Neurol Neurosurg Psychiatry 1986; 49: 867-73.
[37] Money J. Love and love sickness. The science of sex, gender difference, and pair bonding. Baltimore: Johns Hopkins University Press; 1980.
[38] Orford J. Hypersexuality: Implications for a theory of dependence. Br J Addict Alcohol Other Drugs 1978; 73(3): 299-310.
[39] Levine MP, Troiden RR. "The myth of sexual compulsivity". J Sex Res 1988; 25: 347-63.
[40] Rinehart NJ, McCabe M P. Hypersexuality: Psychopathology or normal variant of sexuality? Sexual and Marital Therapy 1997; 12: 45-60.
[41] Quadland MC. Compulsive sexual behavior: Definition of a problem and an approach to treatment. J Sex Marital Ther 1985; 11: 121-32.
[42] Blais-Lecours S, Vaillancourt-Morel MP, Sabourin S, Godbout N. Cyberpornography: Time use, perceived addiction, sexual functioning, and sexual satisfaction. Cyberpsychol Behav Soc Netw 2016; 19: 649-55.
[43] Daneback K, Træen B, Mansson S-A. Use of pornography in a random sample of Norwegian heterosexual couples. Arch Sex Behav 2009; 38(5): 746-53.
[44] Griffiths MD. Internet sex addiction: A review of empirical research. Addict Res Theory 2012; 20: 111-24.
[45] Hald GM, Malamuth NM. Self-perceived effects of pornography consumption. Arch Sex Behav 2008; 37: 614-25.
[46] Person C. Pornography: ''Soft-core''liberalization of indecent material in Europe. In Knill C, Adam C, Hurka S, eds On the road to permissiveness? Change and convergence of moral regulation in Europe. Oxford, UK: Oxford University Press; 2015. p. 102-28.
[47] Regnerus M, Gordon D, Price J. Documenting pornography use in America: a comparative analysis of methodological approaches. J Sex Res 2016; 53: 873-81.
[48] Short MB, Black L, Smith AH, Wetterneck CT, Wells DE. A review of Internet pornography use research: methodology and content from the past 10 years. Cyberpsychol Behav Soc Netw 2012; 15: 13-23.
[49] Remington GJ, Jeffries JJ. Erotomanic delusions and electroconvulsive therapy: a case series. J Clin Psychiatry 1994; 55: 306-8.
[50] Seeman MV. Erotomania and recommendations for treatment. Psychiatr Q 2015; 87: 355-64.
[51] Bancroft J. Sexual behavior that is "out of control": A theoretical conceptual approach. Psychiatr Clin North Am 2008; 31: 593-601.
[52] Friedrich WN, Lysne M, Sim L, Shamos S. Assessing sexual behavior in high-risk adolescents with the Adolescent Clinical Sexual Behavior Inventory (ACSBI). Child Maltreatment 2004; 9: 239-50.
[53] Friedrich WN, Sandfort TGM, Oostveen J, Cohen-Kettenis PT. Cultural differences in sexual behavior: 2–6-year-old Dutch and American children. Journal of Psychology and Human Sexuality 2000; 12: 117-29.
[54] Kafka MP, Hennen J. A DSM-IV axis I comorbidity study of males (n=120) with paraphilias and paraphilia-related disorders. Sex Abuse 2002; 14: 349-66.
[55] Kuzma JM, Black DW. Epidemiology, prevalence, and natural history of compulsive sexual behavior. Psychiatric Clinics of North America 2008; 31: 603-11.
[56] Reid RC. How should severity be determined for the DSM-5 proposed classification of hypersexual disorder? J Behav Addict 2015; 4: 221-5.
[57] Bancroft J. Human Sexuality and Its Problems. 3rd ed. Oxford, England: Elsevier; 2009.
[58] Organization WH. International statistical classification of diseases and related health problems. 10th ed. Geneva 2007.
[59] Lippe S, Gonin-Flambois C, Jambaqué I. Review. The neuropsychology of the Klüver-Bucy syndrome in children. Handb Clin Neurol 2013; 112: 1285-8.
[60] Heare MR, Barsky M, Faziola LR. A Case of mania presenting with hypersexual behavior and gender dysphoria that resolved with valproic acid. Ment Illn 2016; 8: 6546.
[61] Kendler KS. The clinical features of mania and their representation in modern diagnostic criteria. Psychol Med 2016; 19: 1-17.
[62] Kopeykina I, Kim HJ, Khatun T, *et al.* Hypersexuality and couple relationships in bipolar disorder: A review. J Affect Disord 2016; 195: 1-14.
[63] Jones MC, Okere K. Treatment of hypersexual behavior with oral estrogen in an autistic male. South Med J 2008; 101: 959-60.
[64] Luef GJ. Epilepsy and sexuality. Seizure 2008; 17: 127-30.
[65] Saleh F. A hypersexual paraphilic patient treated with leuprolide acetate: a single case report. J Sex Marital Ther 2005; 31: 433-4.
[66] Ong WM, Kulkarni J. Paradoxical hypersexuality in depression. Aust N Z J Psychiatry 2015; 49: 297-8.

[67] Raymond NC, Coleman E, Miner MH. Psychiatric comorbidity and compulsive/impulsive traits in compulsive sexual behavior. Compr Psychiatry 2003; 44: 370-80

[68] Black DW, Kehrberg L, Flumerfelt DL, Schlosser SS. Characteristics of 36 subjects reporting compulsive sexual behavior. Am J Psychiatry 1997; 154(2): 243-9.

[69] Spauwen LWL, Niekamp AM, Hoebe CJPA, Dukers-Muijrers NHTM. Drug use, sexual risk behaviour and sexually transmitted infections among swingers: A cross-sectional study in the Netherlands. Sex Transm Infect 2015; 91: 1.

[70] Jia ZJ, Yan SY, Bao YP, Lian Z, Zhang H, Liu ZM. Sexual behavior differences between amphetamine-type stimulants users and heroin users. Journal of Addiction Medicine 2013; 7: 422-7.

[71] Carpenter BN, Reid RC, Garos S, Najavits LM. Personality disorder comorbidity in treatment-seeking men with hypersexual disorder. Sexual Addiction & Compulsivity 2013; 20: 79-90.

[72] Silverstone T. Dopamine in manic depressive illness. A pharmacological synthesis. J Affect Disord 1985; 8: 225-31.

[73] Ivanco L, Bohnen N. Effects of donepezil on compulsive hypersexual behaviour in Parkinson disease: a single case study. Am J Ther 2005; 12: 467-8.

[74] Britton KR. Medroxyprogesterone in the treatment of aggressive hypersexual behavior in traumatic brain injury. Brain Inj 1998; 12: 703-7.

[75] Huong LM, Rosdinom R. Hypersexuality in dementia: A case report. ASEAN J Psychiatry 2013; 14: 170-4.

[76] Wallace M, Safer M. Hypersexuality among cognitively impaired older adults. Geriatr Nurs 2009; 30: 230-7.

[77] Krueger RB, Kaplan MS. Disorders of sexual impulse control in neuropsychiatric conditions. Semin Clin Neuropsychiatry 2000; 5: 266-74.

[78] Briken P, Habermann N, Berner W, Hill A. Diagnosis and treatment of sexual addiction: A survey among german sex therapists. Sexual Addiction & Compulsivity 2007; 14: 131-43.

[79] Finlayson AJR, Sealy J, Martin PR. The Differential Diagnosis of Problematic Hypersexuality. Sexual Addiction and Compulsivity 2011; 8: 241-51.

[80] Coleman-Kennedy C, Pendley A. Assessment and diagnosis of sexual addiction. J Am Psychiatric Nurses Association 2002; 8: 143-51.

[81] McPherson S, Clayton S, Wood H, Hiskey S, Andrews L. The role of childhood experiences in the development of sexual compulsivity, sexual addiction & compulsivity. The Journal of Treatment & Prevention 2013; 20: 259-78.

[82] Bergner R. Sexual compulsion as attempted recovery from degradation: theory and therapy. J Sex Marital Ther 2002; 28(5): 373-87.

[83] Kaplan MS, Krueger RB. Diagnosis, assessment and treatment of hypersexuality. J Sex Res 2010; 47: 181-98.

[84] Gore-Felton C, Koopman C. Traumatic experiences: harbinger of risk behavior among HIV-positive adults. J Trauma Dissociation 2002; 3: 121-35.

[85] Giugliano J, doi: -. Sexual Addiction: Diagnostic Problems. International Journal of Mental Health and Addiction 2009; 7: 283-94.

[86] Raviv M. Personality characteristics of sexual addicts and pathological gamblers. J Gambling Stud 1993; 9: 17.

[87] Dickinson A. Actions and habits: the development of behavioural autonomy. Philos Trans R Soc Lond Ser B Biol Sci 1985; 308: 67-78.

[88] Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001; 24: 167-2002.

[89] Quirk G, Russo GK, Barron J, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. J Neurosci 2000; 16: 6225-31.

[90] Rogers R, Ramanani N, Mackay C, *et al.* Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. Biol Psychiatry 2004; 55: 594-602.

[91] Claassen DO, van den Wildenberg WP, *et al.* The risky business of dopamine agonists in Parkinson disease and impulse control disorders. Behav Neurosci 2011; 125: 492-500.

[92] Voon V, Mole TB, Banca P, *et al.* Neural correlates of sexual cue reactivity in individuals with and without compulsive sexual behaviours. PLoS One 2014; 9: e102419.

[93] Rolls ET, Kelly PH, Shaw SG. Noradrenaline, dopamine, and brain-stimulation reward. Pharmacol Biochem Behav 1974; 2: 735-40.

[94] Stahl SM. The psychopharmacology of sex, Part 1: Neurotransmitters and the 3 phases of the human sexual response. J Clin Psychiatry 2001; 62: 80-1.

[95] Pfaus JG. Pathways of sexual desire. J Sex Med 2009; 6: 1506-33.

[96] Stahl SM. Stahl's essential psychopharmacology. 3rd ed. New York: Cambridge University Press; 2008.

[97] Meyerson BJ. The effect of neuropharmacological agents on hormone-activated estrus behaviour in ovariectomised rats. Arch Int Pharmacodyn Ther 1964; 150: 4-33.

[98] Fernandez-Guasti A, Escaalante AL, Ahlenius S, Hillegaart V, Larsson K. Stimulation of 5- HT1A and 5-HT1B receptors in brain regions and its effects on male rat sexual behaviour. Eur J Pharmacol 1992; 210: 121-9.

[99] Holstege G, Georgiadis JR, Paans AMJ, Meiners LC, van der Graaf FHCE, Reinders A ATS. Brain activation during human male ejaculation. J Neurosci 2003; 23: 9185-93.

[100] Komisaruk BR, Whipple B. Functional MRI of the brain during orgasm in women. Annu Rev Sex Res 2005; 16: 62-86.

[101] Komisaruk BR, Wise N, Frangos E, Birbano W, Allen K. An fMRI video animation time-course analysis of brain regions activated during self-stimulation to orgasm in women. Poster No. 495.03/SS27. Neuroscience Meeting Planner 2011.

[102] Komisaruk BR, Whipple B, Crawford A, *et al.* Brain activation during vaginocervical self-stimulation and orgasm in womenwith complete spinal cord injury: fMRI evidence of mediation by the vagus nerves. Brain Res 2004; 1024: 77-88.

[103] Frank MJ, Seeberger LC, O'reilly RC. By carrot or by stick: Cognitive reinforcement learning in parkinsonism. Science 2004; 306: 1940-3.

[104] Guthrie M, Myers CE, Gluck MA. A neurocomputational model of tonic and phasic dopamine in action selection: A comparison with cognitive deficits in parkinson's disease. Behav Brain Res 2009; 200: 48-59.

[105] Feduccia AA, Chatterjee S, Bartlett SE. Neuronal nicotinic acetylcholine receptors: neuroplastic changes underlying alcohol and nicotine addictions. Front Mol Neurosci 2012; 3: 83.

[106] Wei W, Rubin JE, Wang XJ. Role of the indirect pathway of the basal ganglia in perceptual decision making. J Neurosci 2015; 35: 4052-64.

[107] Luo SX, Huang EJ. Dopaminergic neurons and brain reward pathways: From neurogenesis to circuit assembly. Am J Pathol 2016; 186: 478-88.

[108] Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. Lancet 2007; 369: 512-25.

[109] Christakou A, Robbins TW, Everitt B. Prefrontal cortical–ventral striatal interactions involved in affective modulation of attentional performance: Implications for corticostriatal circuit function. J Neurosci 2004; 4: 773-80.

[110] Floresco SB, Braaksma D, Phillips AG. Thalamic-cortical-striatal circuitry subserves working memory during delayed responding on a radial arm maze. J Neurosci 1999; 24: 11061-71.

[111] Huang H, Ghosh P, van den Pol A. Prefrontal cortex–projecting glutamatergic thalamic paraventricular nucleus-excited by hypocretin: A feedforward circuit that may enhance cognitive arousal. J Neurophysiol 2005; 95: 1656-68.

[112] Marsh ABK, Vythilingam M, Busis S, Blair R. Response options and expectations of reward in decision-making: The differential roles of dorsal and rostral anterior cingulate cortex. NeuroImage 2007; 35.

[113] Wall P, Flinn J, Messier C. Infralimbic muscarinic M1 receptors modulate anxiety-like behaviour and spontaneous working memory in mice. Psychopharmacology (Berl) 2001; 155: 58-68.

[114] Gehring WJ, Knight RT. Prefrontal-cingulate interactions in action monitoring. Nat Neurosci 2000; 3: 516-20.

[115] Dalley J, Cardinal R, Robbins T. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neuroscience and Biobehavioral Reviews 2004; 28: 771-84.

[116] Everitt BJ, Robbins TW. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci 2005; 8: 1481-9.

[117] Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. Neuron 2000; 28: 343-7.

[118] Reuter JRT, Rose M, Hand I, Glascher J, Buchel C. Pathological gambling is linked to reduced activation of the mesolimbic reward system. Nature Neuroscience 2005; 8: 147-8.

[119] Davis JF, Loos M, Di Sebastiano AR, Brown JL, Lehman MN, Coolen LM. Lesions of the medial prefrontal cortex cause maladaptive sexual behavior in male rats. Biol Psychiatry 2010; 67: 1199-204.
[120] Anglada-Figueroa D, Quirk GJ. Lesions of the basal amygdala block expression of conditioned fear but not extinction. J Neurosci 2005; 25: 9680-85.
[121] Everitt BJ, Caddor M, Robins TW. Interactions between the amygdala and ventral striatum in stimulus-reward associations: Studies using a second-order schedule of sexual reinforcement. Neuroscience and Biobehavioral Reviews 1989; 30: 63-75.
[122] Pitkanen A. Connectivity of the rat amygdaloid complex. In: JP A, editor. The amygdala: A functional analysis. Oxford, UK: Oxford Univ Press; 2000.
[123] Masco DH, Carrer HF. Sexual receptivity in female rats after lesion or stimulation in different amygdaloid nuclei. Physiology & Behavio 1980; 24: 1073-80.
[124] Baird AD, Wilson SJ, Bladin PB, Saling MM, Reutens DC. The amygdala and sexual drive: Insights from temporal lobe resection in intractable epileps. Ann Neurol 2004; 55: 87-96.
[125] Ferretti A, Caulo M, Del Gratta C, *et al.* Dynamics of male sexual arousal: distinct components of brain activation revealed by fMRI. Neuroimage 2005; 26: 1086-96.
[126] Hamann S, Herman RA, Nolan CL, Wallen K. Men and women differ in amygdala. Nat Neurosci 2004; 7: 411-6.
[127] Klüver H, Bucy PC. Preliminary analysis of functions of the temporal lobes in monkeys. Arch Neurol Psychiatry 1939; 42: 979-1000.
[128] Giantonio GW, Lund NL, Gerall AA. Effect of diencephalic and rhinencephalic lesions on the male rat's sexual behavior. J Comp Physiol Psychol 1970; 73: 38-46.
[129] Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. Brain Res Brain Res Rev 2003; 41: 88-123.
[130] Baird AD, Wilson SJ, Bladin PF, Saling MM, Reutens DC. Neurological control of human sexual behaviour: insights from lesion studies. J Neurol Neurosurg Psychiatry 2007; 78: 1042-9.
[131] Guarraci FA, Bolton J L. "Sexy stimulants": The interaction between psychomotor stimulants and sexual behavior in the female brain. Pharmacology, Biochemistry, and Behavior 2014; 121.
[132] Wainberg ML, Muench F, Morgenstern J, *et al.* A double-blind study of citalopram *versus* placebo in the treatment of compulsive sexual behaviors in gay and bisexual men. J Clin Psychiatry 2006; 67: 1968-73.
[133] Kafka MP, Prentky R. Fluoxetine treatment of nonparaphilic sexual addictions and paraphilias in men. J Clin Psychiatry 1992; 53: 351-8.
[134] Ozkan B, Wilkins K, Muralee S, Tampi RR. Pharmacotherapy for inappropriate sexual behaviors in dementia: a systematic review of literature. Am J Alzheimers Dis Other Demen 2008; 23: 344-54.
[135] Kafka MP, Coleman E. Serotonin and paraphilias: the convergence of mood, impulse and compulsive disorders. J Clin Psychopharmacol 1991; 11: 223-4.
[136] Kruesi MJ, Fine S, Valladares L *et al.* Paraphilias: a doubleblind crossover comparison of clomipramine *versus* desipramine. Arch Sex Behav 1992; 21: 587-93.
[137] Casals-Ariet C, Cullen K. Exhibitionism treated with clomipramine. Am J Psychiatry 1993; 150: 1273-4.
[138] Torres AR, Cerqueira AT. Exhibitionism treated with clomipramine [letter]. Am J Psychiatry 1993; 150: 1274.
[139] Wawrose FE, Sisto TM. Clomipramine and a case of exhibitionism [letter]. AmJ Psychiatry 1992; 149: 843.
[140] Coleman E, Cesnik J, Moore A-M, Dwyer SM. An exploratory study of the role of psychotropic medication in the treatment of sex offenders. J Offender Rehab 1992; 18.
[141] Kuzma JM, Black DW. Compulsive disorders. Curr Psychiatry Rep 2004; 6: 58-65.
[142] Nishimura H, Suzuki M, Kazahara H, Ushijima S. Efficacy of lithium carbonate on public and compulsive masturbation: a female case with mild mental disability. Psychiatry Clin Neurosci 1997; 51: 411-3.
[143] Chughtai B, Sciullo D, Khan S, Rehman H, Mohan E, Rehman J. Aetiology, diagnosis & management of Hypersexuality: A review. Int J Urol 2009; 6.
[144] Rosler A, Witztum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. N Engl J Med 1998; 338: 416-22.
[145] Cooper AJ. A placebo-controlled trial of the antiandrogen cyproterone acetate in deviant hypersexuality. Comprehensive Psychiatry 1981; 22: 458-65.
[146] Meyer WJ, Cole C, Emory E. Depo provera treatment for sex offending behavior: An evaluation of outcome. Bull Am Acad Psychiatry Law 1992; 20: 249-59.
[147] Light SA, Holroyd S. The use of medroxyprogesterone acetate for the treatment of sexually inappropriate behaviour in patients with dementia. J Psychiatry Neurosci 2006; 31: 132-4.
[148] Krueger RB, Kaplan MS. Depot-Leuprolide acetate for treatment of paraphilias: A report of twelve cases. Arch Sex Behav 2001; 30: 409-22.
[149] Krueger RB, Kaplan MS. Behavioral and psychopharmacological treatment of the paraphilic and hypersexual disorders. J Psychiatr Pract 2002; 8: 21-32.
[150] Garcia FD, Thibaut F. Current concepts in the pharmacotherapy of paraphilias. Drug 2011; 71: 771-90.
[151] Belchetz PE, Plant TM, Nakai Y, Keogh EJ, Knobil E. Hypophysial responses to continuous and intermittent delivery of hypothalamic gonadotropin-releasing hormone. Science 1978; 202: 631-3.
[152] McEvoy G. AHFS drug information. Bethesda, MD: American Society of Health System Pharmacists; 1999.
[153] Thibaut F, Cordier B, Kuhn JM. Effect of a long-lasting gonadotrophin hormone-releasing hormone agonist in six cases of severe male paraphilia. Acta Psychiatr Scand 1993; 87: 445-50.
[154] Czerny JP, Briken P, Berner W. Antihormonal treatment of paraphilic patients in German forensic psychiatric clinics. Eur Psychiatry 2002; 17: 104-6.
[155] Thibaut F, Cordier B, Kuhn JM. [Drug modulation of libido and sexual activity. Behavior effect of GnRH analog in man]. [Article in French] Ann Endocrinol (Paris) 1994; 55: 229-33.
[156] Grant JE, Kim SW. A case of kleptomania and compulsive sexual behavior treated with naltrexone. Ann Clin Psychiatry 2001; 13: 229-31.

PMID: 28325146