Chapter

Sexual Dysfunction in Neurological Disorders with Special Emphasis on Parkinson's Disease: Insights from Clinical Studies and Animal Models

Zevelou Koza, Padmanabhan S. Rajani, Muralidhara, Ajaikumar B. Kunnumakkara and Sarat Chandra Yenisetti

Abstract

Epidemiological studies illustrate that sexual dysfunction (SD) is common among the majority of patients suffering from neurological disorders (NLDs). However, our understanding of the SD in NLDs is in its infancy. Our effort in this review article reveals how the clinical studies illustrate different phenotypes relating to SD in both men and women suffering from NLDs, with special reference to PD, and how the development of animal models will provide a fantastic opportunity to decipher mechanistic insights into the biological and molecular processes of SD, understanding of which is critical to figure out the causes of SD and to develop therapeutic strategies either by targeting molecular players or altering and/or regulating the profiles of involved genetic targets. Specific emphasis is placed on dopamine-dependent and independent mechanism(s) of SD among PD patients, which is important because certain critical dopamine-independent phenotypes are yet to be characterized and understood in order to decipher the comprehensive pathophysiology of PD. Synergic efforts of both clinicians and bench scientists in this critical direction would significantly improve the quality of life of sufferers of NLDs who are already burdened. This knowledge relating to SD will help us to make one more step in reducing the burden of disease.

Keywords: sexual dysfunction, neurodegenerative disorders, Parkinson's disease, dopamine, animal models, drosophila, rat, mice

1. Introduction

In humans, sexual behavior is classified into two main activities: sexual desire and sexual arousal. Sexual desire is represented by libido/sexual drive [1], whereas sexual arousal is the ability to respond to an appropriate sexual stimulus with a sequence of stereotyped vascular, neural, and muscular reactions [2]. The typical sexual response cycle of men consists of libido, erection, ejaculation, orgasm, and

detumescence [3]. In women, the sexual cycle follows a parallel framework as in men, such as libido, arousal, orgasm, and satisfaction [4]. A problem occurring during any phase of this sexual response cycle, which prevents the individual from experiencing satisfaction from the sexual activity, is referred to as sexual dysfunction (SD). The human sexual response cycle, therefore, sets the foundation for studying and categorizing SD in men and women. As reported by Hatzimouratidis and Hatzichristou [5], numerous measures have been taken since 1992 to define and classify SD in a precise manner. Although a number of classification systems were proposed for SD, the two most widely used classification systems are the International Classification of Diseases (ICD)-10 provided by the World Health Organization [6] and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV provided by the American Psychiatric Association [7]. The four major categories of SD as described by both systems include disorders of sexual desire/interest, arousal, orgasm, and sexual pain.

These dysfunctions of sexual function are extremely common in patients with neurological disorders (NLD). NLDs are diverse forms of central nervous system disorders distinguished by the continuing loss of neural tissues because they alter the normal sexual functions in both men and women patients [8].

2. Prevalence of sexual dysfunction in neurological disorders

Disorders of sexual function are common among men of all ages, ethnicities, and cultural backgrounds. SD is highly prevalent in both sexes, ranging from 10 to 52% of men and 25 to 63% of women [9–11]. It is reported that more than 18 million men in the United States alone and 40 million men in the European Union are affected by erectile dysfunction (ED), and individuals suffering from this dysfunction are estimated to reach 322 million by 2025. Aberrant sexual function is reported in several diseases, namely, arterial hypertension, diabetes, metabolic syndrome, coronary diseases, neurological diseases (stroke, epilepsy, multiple sclerosis, Parkinson's disease), and psychiatric disorders [12]. Below are some of the neurological disorders and the prevalence of SD in these patients.

2.1 Multiple sclerosis

Multiple sclerosis (MS) is a continual inflammatory demyelinating disease of the central nervous system along with the presence of relapsing–remitting attacks of inflammation, demyelination, and axonal damage, causing a broad spectrum of neurological symptoms and impairment both in men and women. The symptoms of MS include weakness and imbalance, visual abnormalities, changes in cognition, bladder, and sexual dysfunction (SD) [13], which affect young adults in their sexually active phase of life [14]. MS occurs due to the integrated effects of genetic, environmental, infectious factors, and vascular problems but chiefly due to an autoimmune mechanism [15].

SD is extremely common in MS sufferers, affecting 40–80% of women and 50–90% of men [16] and has an adverse impact on the quality of life (QoL) of these patients. Although SD is a painful symptom, most often it goes underreported and underdiagnosed in MS, because of the patients and physicians' reluctance with the topic [17]. The symptoms of SD in MS men include ED, ejaculatory dysfunction,

orgasmic dysfunction, and reduced libido [17]. Whereas low libido, orgasmic dysfunction, reduction in the tactile sensations originating from the thigh and genital regions, and vaginal dryness with subsequent dyspareunia (difficulty in sexual activity) are some of the sexual symptoms in MS women [18]. SD in MS is mainly due to the lesions affecting the neural pathways involved in physiologic function and also the psychological impact of the disease on the patients [14]. All these studies show that SD is highly prevalent in MS patients, and there is a need for both the patients and the neurologist to discuss more about this symptom, which otherwise is neglected.

2.2 Epilepsy

Epilepsy is the most prevalent chronic NLD, represented by an episodic seizure that demands lifelong management with medication [19]. Mameniškienė et al. [20] reported in their study the high prevalence of sexual problems in one third of epileptic patients and only a quarter of them seeking medical help. Dysfunctions such as decrease in sexual desire, potency, orgasm, and ED were reported by male epileptic patients [21]. Sexual symptoms in epileptic women include decreased sexual arousal, vaginismus, and dyspareunia [22]. The most common SD in males were ED and early ejaculation, whereas female's lack of sexual interest and failure to reach orgasm were the most common sexual problems based on several studies on epilepsy [23].

The cause of SD in epileptic patients is multifactorial in nature, such as the effects of antiepileptic drugs on neurotransmission, the epilepsy itself, and psychosocial factors associated with it, but the presence of hormonal changes in epileptic patients is believed to be one of the prominent factors for SD [24]. All these studies illustrate the common presence of SD in both male and female epileptic patients and highlight the multifactorial nature of this dysfunction.

2.3 Multiple system atrophy

Multiple system atrophy (MSA) is a progressive neurodegenerative disease of unspecified etiology, affecting both males and females [25]. Symptoms of the disease include motor symptoms (gait, coordination, and muscle tone) and non-motor features (cardiovascular, gastrointestinal, genitourinary, sleep disorders, cognitive, mood, and behavioral problems, dysphagia, SD, and visual abnormalities [26]). SD such as impairment in ED was reported to be the first symptom of the disease in men [27]. In another study, reduced genital sensitivity in female MSA patients was one of the early manifestations of the disease [28]. Sexual problems in MSA are believed to be due to abnormalities in the central and peripheral nervous systems in MSA patients [29]. All these studies elucidate the importance of SD in the early diagnosis of the disease.

2.4 Huntington's disease

Huntington's disease (HD) is a chronic disabling disease caused by a single defective gene on chromosome 4 affecting the basal ganglia region of the brain and is linked with aberrant sexual behaviors. A total of 85% of men and 75% of women complain of sexual problems, such as hypoactive and hyperactive sexual disorders and paraphilia in certain cases [30]. Huntington's female patients suffer from sexual

problems, such as difficulty in arousal, lubrication, orgasm, and sexual dissatisfaction, that impair their quality of life [31]. Whereas in male patients, problems with erection, reduced sexual desire, and performance are some of the common sexual problems [32]. SD in HD is reported to be due to the progression of the disease and its associated symptoms, such as depression or dementia, the decline in patient's motor functions, and side effects of medication [31]. Although only a few studies have been conducted on sexuality in HD, all these studies show that SD is extremely common in these patients and that sexual disorders may take the form of hypoactive to increased sexual interest or paraphilias.

2.5 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive disorder of motor neurons in the brain and spinal cord [33]. ALS patients were found to have problems with their sexual relationship due to impaired sexual function such as decreased libido [34], with studies indicating that ALS had the worst rates of SD when compared with other NLDs [35]. Shahbazi et al. [36] reported that although SD affected the QoL in ALS patients, 75% of their clinicians were not familiar with any strategies or interventions to help the patients. This shows the need to further explore sexuality in both ALS men and women. The change in sexual functions in ALS patients was due to the physical and psychosocial factors associated with the disease [34]. All these studies show that sexuality in patients with ALS has received little attention, and sexual function is rarely assessed in both male and female ALS patients.

2.6 Schizophrenia

Schizophrenia is a severe psychiatric disorder that attacks close to about 1% of the world's population with no concrete etiology [37]. The neurodevelopmental postulation of schizophrenia caused by genetics or environmental elements is one of the glaring reasons for the disease, which leads to the alteration of important and fine signaling pathways, resulting in the initial presentation of the disease [38]. It is identified by positive symptoms such as delusions and hallucinations, negative symptoms such as emotional withdrawal and apathy, and cognitive deficits such as impaired attention, learning, and memory [39]. The age of onset of schizophrenia in men is between the ages of 16 and 25 years, and in women from 25 to 35 years.

Schizophrenia affects individuals at their prime reproductive age, with a negative impact on sexual functions of both male and female patients [40]. The extensiveness of SD in schizophrenic patients was 31.1–82.7%. In males, the prevalence of SD was 82–84.5%; and in female patients, the prevalence was 78.6–92% [41]. Reduced sexual desire was frequently reported by the patients [42]. Dysfunction such as ED (95.2%) was the most common complaint in men followed by pleasure dysfunction (94.2%). In female patients, pleasure dysfunction (94.7%) was the most prevalent SD followed by arousal/excitement dysfunction (93.2%) [41]. The use of antipsychotic medication is believed to be one of the important causes of SD. Postsynaptic dopamine antagonism, prolactin elevation, and α1-receptor blockade are some of the factors behind the pathogenesis of antipsychotic-induced SD [40]. All these studies illustrate the high existence of SD in both male and female schizophrenic patients and its negative impact on the quality of life of these young patients.

2.7 Alzheimer's disease

Alzheimer's disease (AD) is one of the most widespread forms of dementia, consisting of 60–70% of all dementia cases [43] and affecting 35 million individuals worldwide with 5.4 million Americans alone [44]. AD has a significant effect on the sexual behavior of the patients [45], and loss of sexual interest and decreased sexual activity are the two common types of sexual disorders in AD patients [46]. Studies have shown that 53% of male AD patients suffer erectile failure or loss of erection [47]. Thus, the onset of the disease affects the relationship between the patient and their partner because of the presence of high sexual dissatisfaction [48]. The cause of this sexual impairment in AD is believed to be due to a decline in the patient's ability to consent, physical vulnerability, depression, anxiety, and medical conditions related to the disease [49]. All these studies show that SD is not uncommon in AD patients, which deteriorates the relationship between patients and their spouses.

2.8 Parkinson's disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder that affects about 1% of the population over the age of 50 [50]. PD was first reported by James Parkinson in 1817, and symptoms such as trembling, difficulty walking and standing, tiredness, sleep disturbances, drooling, difficulty swallowing, gastrointestinal dysfunction, and bladder dysfunction were all described by James Parkinson in his early study [51]. Today, symptoms of PD are classified into motor and non-motor symptoms (NMS). Motor problems such as resting tremors, bradykinesia, rigidity, and postural abnormalities [52] are some of the symptoms with which clinicians diagnose PD. However, over the years, the NMS of PD has gained a lot of interest because several studies have supported that non-motor issues preceded the motor manifestation of the disease [53] and may even project the future development of PD years or even decades earlier than a motor-based diagnosis [54]. The spectrum of NMS in PD includes loss of sense of smell, rapid eye movement (REM) sleep disturbances, daytime drowsiness, delusions, difficulty in concentration, drooling, difficulty swallowing, episodes of confusion, fatigue, impulse control disorders (ICDs), memory problems, depression and anxiety, pain paranoia, sensation of breathlessness, sweating, postural hypotension, urinary problems, gastrointestinal dysfunction, and SD [55].

Data from a number of studies report the prevalence of non-motor disorders affecting PD patients [56], but unless specifically investigated, it goes unreported with no adequate treatment available [57]. Epidemiological studies of non-motor symptoms of PD such as the presence of REM sleep behavior disorder, olfactory dysfunction, urinary disorder, and constipation [58] are known to clearly increase the future chance of developing PD. Symptoms such as constipation, anxiety disorders, RBD, and anemia were shown to precede the motor dysfunction by at least 20 years, whereas olfactory impairment and depression preceded the motor symptoms with a lag time of 2 to 10 years [53]. Therefore, such studies show that NMS of PD can play an important role as a predictive biomarker for the identification of a population at greater risk of developing the disease.

3. Sexual dysfunction in Parkinson's disease subjects

Sexual dysfunction in men is generally defined as the inability to achieve or maintain an erection until the completion of sexual activity. Whereas in women, SD is the

disruption in sexual desire and in the psychophysiological changes that identify the sexual response cycle and cause marked distress and interpersonal difficulty [7]. SD is one of the most common non-motor disorders affecting Parkinsonian patients [59]. Although SD remains one of the prominent symptoms of PD, it is the most neglected, underreported, and under-recognized aspect of PD [59].

Singer and colleagues [60] conducted the first study on PD men to show that these men had worse sexual problems when compared with non-Parkinsonian healthy individuals. Thereafter, several studies have reported the widespread presence of sexual impairments in Parkinsonian patients [61, 62]. Some of the most common sexual malfunctions in PD men were a decrease in libido/ loss of sexual interest, decrease in frequency of sexual intercourse, decrease in orgasm/inability to experience orgasm/ orgasmic dissatisfaction, decrease in erection/ED, difficulties/delayed in ejaculation, premature ejaculation [59, 62]. In PD women, the sexual impairment ranged from decrease in libido/loss of sexual interest, decrease in frequency of sexual intercourse, inability to experience orgasm/difficulty reaching orgasm, orgasmic dissatisfaction, difficulty with arousal, and dyspareunia [61, 62]. All these studies and findings in PD subjects indicate the extent of sexual impairments in PD sufferers and the urgency of effective therapeutic intervention in the management of SD in PD. The nature of SD among male and female patients and its prevalence are elaborated in **Table 1**.

SD, such as ED, was shown to act as an early marker for detection of individuals who are at higher risk of developing PD in the near future. A study conducted by

Sexual dysfunction in PD men		
Nature of sexual problems	**Prevalence in PD patients**	**References**
Erectile dysfunction (ED)	42.6–79%	[60, 61, 63, 64]
Premature ejaculation	40.6%–51.4%	[61, 62]
Difficulties ejaculating	27.3–79%	[61, 64]
Difficulties reaching orgasm	39.5–87%	[61, 63]
Low sexual desire	23.3–84%	[61, 63–65]
Reduced sexual activity	33.4–55%	[63, 65]
Dissatisfaction with sexual life	59–65.1%	[61, 66]
Sexual dysfunctions in PD women		
Nature of Sexual Problems	Prevalence in PD patients	References
Dyspareunia (painful sex)	12.5%	[61]
Difficulties in getting aroused	87.5%	[61]
Difficulties reaching orgasm	72–75%	[61, 62]
Low sexual desire	46.9–83%	[61, 63, 65]
Orgasmic Dissatisfaction	76%	[62]
Reduced sexual activity	75–88%	[63–65]
Dissatisfaction with sexual life	36–37.5%	[61, 66]

Table 1.
Nature of sexual dysfunction in Parkinson's disease patients.

[67] reported that individuals with ED were 3.8-fold more likely to develop PD when compared to subjects without ED. Medical record review found that ED was more prevalent in individuals who later developed PD compared with non-PD individuals at 5 years and 2 years prior to diagnosis [68]. In PD patients with idiopathic RBD, ED was noticed 7 years before the disease conversion, with an extrapolated prodromal interval of 11 years [69]. Thus, the above studies show that sexual malfunction such as ED is a good marker for early detection of individuals at risk of developing PD. Therefore, people with any type of SD must take preventive measures and check for necessary assistance.

4. Factors responsible and insights into the mechanism of sexual dysfunction in Parkinson's disease

4.1 Age

In PD, advancing age of an individual is one of the major risk factors for the development and progression of the disease [70]. Even in the absence of any clinical or medical conditions, aging process was shown to play a key role in the development of SD such as a decrease in potency and ED [71]. However, a study conducted on PD patients and non-PD individuals shows that with age, sexual function was worse in PD patients than in the normal elderly population [72]. In addition, in aged PD patients, disease severity or disease duration did not have any effect on PD-related changes in sexual function [73]. Thus, all these studies suggest that SD is more prevalent in the PD population, and age has little effect on the sexual function of these patients.

Dysfunction in normal sexual functions is not only limited to aging Parkinson's patients but also young PD individuals were reported to be affected more often by this dysfunction [8, 70, 73]. In addition, SD was one of the greatest concerns of the disease in young patients [74]. Another study was conducted to see the effect of PD's age of onset on the sexual function of the patients and reported that 59% of early-onset PD (EOPD) patients suffer from sexual problems as compared to 80.3% of late-onset PD (LOPD) patients [75]. Thus, suggesting that SD is not only limited to aging Parkinson's patients but also very prevalent even in young PD patients.

4.2 Involvement of dopamine and dopaminergic pathways

Dopamine (DA), the chief neurotransmitter in the central nervous system (CNS), plays a role in facilitating sexual motivation, copulation, and genital reflexes [76] by regulating sexual behaviors through the determination of the strength of libido, arousal, and erection. Early clinical studies show that l-3, 4-dihydroxyphenylalanine (L-DOPA), the precursor of DA, induces penile erection in men with PD [77], supporting the involvement of DA in sexual behavior. However, disruptions in the hypothalamic area in PD in relation to SD have not been well studied [62]. Moreover, the use of various DA agonists in animal models for the treatment of SD provides strong evidence of the involvement of the dopaminergic system in the control of sexual function in mammals such as humans.

Below are the several studies done on animal models to show the involvement of DA in the normal sexual function:

4.2.1 Rat model

Rat models were used to understand the SD caused by death in the dopaminergic neurons of the *substantia nigra* (SN). In rats, the central dopaminergic neurons project in the medial preoptic area and paraventricular nucleus and travel from the hypothalamus to the lumbosacral spinal cord, controlling both the autonomic and somatic components of penile reflexes [78]. Experimental rats injected with 6-hydroxydopmaine, a DA antagonist, mimic PD by destroying dopaminergic SN cells. These rats showed a decrease in the number of erections and a complete absence of SN *pars compacta* in the brain when compared to normal rats. Quantification of DA and its metabolites using HPLC (high-performance liquid chromatography) also showed a significant decline in their levels in both hemispheres of the brain, with a significant reduction in the right hemisphere when compared to normal rats [79]. As also shown, the right hemisphere is involved in the sexual functions of mammals including humans [80]. This study suggests DA in the hemisphere plays a vital role in the observed SD in the rat models and could likely be the possibility among human PD patients.

Several other studies show that DA antagonist inhibits sexual behaviors such as copulation, genital reflexes, and sexual motivation in rats [81]. Whereas DA agonists restored the copulation activity of male rats by reducing the latency of ejaculation, producing spontaneous ejaculation and enhancing penile erection [18]. Male rats with 6-hydroxydopamine or radiofrequency lesions in the nucleus accumbens showed a low incidence of noncontact erection, indicating the role of DA in arousal processes in responding to remote cues from estrous females [82]. All these studies suggest that DA is the crucial neurotransmitter in the regulation of sexual functions involved in both sexual motivation and sexual performance, which is likely the case in humans.

4.2.2 Mice model

A study was done on a mice model to show the effect of DA and its agonist on the sexual behavior of the mice. DA was shown to influence the rewarding aspects of intromissions in both male and female mice, and DA receptors were essential for the actions of DA on the receptivity of male and female sexual behavior [83]. Apomorphine, a DA agonist shows pro-erectile effects (erection, erection-like responses, and genital grooming) in mice models by activating the central dopaminergic receptors (D2) [84]. All these studies illustrate that dopamine agonists can be a possible therapeutic agent to address ED-related SD in PD subjects.

4.2.3 Drosophila model

Study using *Drosophila* as model animal has shown that dopamine regulates the male courtship intensity via the dopaminergic neurons PPL2ab (protocerebral posteriolateral dopaminergic cluster neuron 2ab); and by increasing the DA levels in these neurons, the decreased courtship activity in aged male flies was reinstated [85]. Kuo and co-workers demonstrated it both quantitatively and qualitatively by observing the behavioral assay of male fly via courtship index (percentage of time spent on courtship behavior), which is a quantitative expression of courtship duration; and courtship bout length (indicates the degree to which the courtship period was fragmented between courtship and non-courtship behavior), which quantifies courtship episode duration. Whereas when DA levels were downregulated, there

was a significant decrease in the courtship index and courtship bout length in males. This study therefore highlights the importance of DA in regulating sexual activity in flies. Disruption in the dopaminergic neurotransmission also shows a significant reduction in the male's courtship behavior towards a female [86]. A *Drosophila* model of SD of PD was first reported by Shaltiel-Karyo et al. [87]. They used the *Drosophila* α-syn model where there is a loss of DA neurons and showed that this male fly has impaired sexual function and performs an overall less sexual activity in the courtship parameters of orientation, wing vibration, licking, attempted copulation, nonsexual encounter, and copulation [87]. All these studies illustrate the direct involvement of dopamine in the regulation of sexual behavior, which is likely the case in humans.

4.3 Non-dopaminergic pathways and sexual dysfunction

Because degeneration of dopaminergic neurons is the critical pathological hallmark associated with PD, I have primarily focused on the involvement of dopaminergic pathways in SD. However, it has been reported that other various factors/pathways are involved in human sexual function. Meston and Frohlich [88] provided a concise review of several factors that influence male and female sexual function such as (a) the endocrine factors: androgens, estrogens, progesterone, prolactin, oxytocin, cortisol, and pheromones; and (b) neurotransmitters and neuropeptides: nitric oxide, serotonin, epinephrine, norepinephrine, opioids, acetylcholine, histamine, and g-aminobutyric acid. In spite of their involvement in sexual function, no detailed information is available whether these factors/pathways are involved in SD of PD.

Of all these non-DA pathways, it has been demonstrated that PD patients over the age of 60 were reported to have low levels of testosterone [89]). Testosterone deficiency encompasses several domains, namely, sexual, physical, psychological, and cognitive. SD such as decreased or lost sexual desire diminished nocturnal and morning erections, and ED are often among the most recognized symptoms of testosterone deficiency [90]. In a case study involving five PD patients over the age of 60 with symptoms of testosterone deficiency, patients experienced significant improvement in their sexual functions following testosterone replacement therapy [91]. A daily dose of transdermal testosterone gel given to PD patients with testosterone deficiency showed improvement in their sexual function such as libido [91]. Apart from this, not much/nothing has been studied about the involvement of other factors with reference to SD in PD.

5. Conclusion and future aspects

SD, such as a decrease in desire and ED, are extremely common in NLD. SD greatly impacts the quality of life of patients and their spouses. Although SD is common in NLDs such as PD, it remains one of the most neglected and understudied symptoms of the disease. SD affects some 80% of PD patients, and the cause of this dysfunction can be multifactorial in nature and a mechanism that is poorly understood to date. However, several studies have implicated the role of dopamine in the regulation of sexual function in a wide variety of animal models including humans. But little progress has been made in the area of exploring sexuality in these diseases, which greatly hampers the overall quality of life of the patients. The multifactorial causes of SD in NLD make it difficult for an effective therapeutic treatment. Further studies to understand the mechanisms of SD in NLD such as PD will greatly help in identifying

therapeutic targets for sexual problems. Here lies the challenge and great opportunity for both clinicians and bench scientists.

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Author details

Zevelou Koza[1], Padmanabhan S. Rajani[2], Muralidhara[2], Ajaikumar B. Kunnumakkara[3] and Sarat Chandra Yenisetti[1*]

1 Drosophila Neurobiology Laboratory, Nagaland University (Central), Nagaland State, India

2 CSIR-Central Food Technological Research Institute (CFTRI), Mysuru, India

3 Cancer Biology Laboratory and DBT-AIST International Laboratory for Advanced Biomedicine (DAILAB), Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Guwahati, Assam, India

*Address all correspondence to: sarat@nagalanduniversity.ac.in; yschandrays@rediffmail.com

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