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Management of sexual dysfunction due to central nervous system disorders: a systematic review

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Objective

To systematically review the management of sexual dysfunction due to central nervous system (CNS) disorders.

Patients and Methods

The review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified independently by two reviewers using electronic searches of MEDLINE and OVID (from January 2004 to August 2014) and hand searches of reference lists and review articles.

Results

In patients with CNS disorders, neuro-urological assessment is recommended for both genders before starting any treatment for sexual dysfunction. For men, blood sexual hormones evaluation is the main investigation performed before phosphodiesterase type 5 inhibitors (PDE5Is) treatment, whereas there is no consensus on routine laboratory tests for women. PDE5Is are the first-line medical treatment for men, with the most robust data derived from patients with spinal cord injury assessed by validated questionnaires, mainly the International Index of Erectile Function-15. There is no effective medical treatment for sexual dysfunction in women. Sacral neuromodulation for lower urinary tract dysfunction may improve sexual dysfunction in both genders.

Conclusions

Although sexual dysfunction is a major burden for patients with CNS disorders, high-evidence level studies are rare and only available for PDE5Is treating erectile dysfunction. Well-designed prospective studies are urgently needed for both genders.

Keywords

neurogenic sexual dysfunction, neurogenic erectile dysfunction, phosphodiesterase type 5 inhibitors

Introduction

Sexual dysfunction in patients affected by neurological disorders has many causes. A conceptual model for sexual problems was initially proposed to characterise three levels of influence in patients with multiple sclerosis (MS): primary, secondary and tertiary sexual dysfunction. Actually this model is valid for all neurological patients and should always be included in the diagnostic algorithm to address the appropriate examinations and therapies for sexual dysfunction as well. Primary sexual dysfunction results from neurological lesions directly affecting the neural pathways subserving sexual function. Neurological diseases affecting the cerebrum, brain stem, spinal cord, spinal roots or peripheral nerves including the autonomic nervous system, can alter sexual function [1,2].

Sexual dysfunction includes decreased or loss in libido, painful or uncomfortable genital sensations (burning, tingling, numbness), and/or altered orgasmic response in both women and men. Women may experience decreased vaginal lubrication and dryness, anorgasmia, and low sex drive [3,4]. Men may have difficulty achieving and/or maintaining an erection, and diminished frequency of ejaculation [5–7]. Secondary sexual dysfunction arises as a consequence of disability caused by poor bladder and bowel control, fatigue, muscle weakness, spasticity, immobility, tremor, cognitive impairment, and sensory problems. Secondary sexual dysfunction can also be a result of non-neurological co-morbidities, e.g. hypertension, diabetes, depression, hypercholesterolaemia, obesity, and chronic smoking. In addition, medications that are used for the neurological conditions (spasticity, urinary frequency, sensory pain, etc.) and non-neurological co-morbidities (hypertension, diabetes, depression, etc.) can further contribute to secondary sexual dysfunction. Tertiary sexual dysfunction is related to psychological, social and cultural issues that affect sexual response. These variables can include anxiety, low self-esteem, altered marital and family roles, changes in body image, and fear of rejection by the partner [8–11]. For each individual

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with a neurological disease, these three levels are interconnected and may fluctuate, interfering with each other continuously throughout life, generating or leading to a worsening of sexual impairments. Before addressing sexual dysfunction in a patient with a neurological disease, attitude towards sex, sexual orientation and cultural influences should be determined. Involvement of the patient's partner is recommended, if appropriate, when the quality of the relationship and the patient/partner needs and expectations of therapy have been assessed. Neurogenic sexual dysfunction often severely disrupts quality of life, so that healthcare professionals must be involved in treating an individual's sexual health [12,13]. In the present study, we aimed to systematically assess the management of sexual dysfunction due to CNS disorders.

Patients and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [14]. Two authors (M.L and S.M.) independently searched MEDLINE and OVID using the following terms: 'neurogenic sexual dysfunction' (OR) 'neurogenic erectile dysfunction' (OR) 'spinal cord', 'multiple sclerosis', 'Parkinson's disease', 'stroke', 'epilepsy', 'spina bifida' (AND) 'sexual dysfunction' (OR) 'erectile dysfunction' (OR) 'sexual function' (AND) 'treatment'. Search criteria were limited to humans, adults, and full-text English articles. All relevant papers published in English from 2004 to 2014 were retrieved. References of selected articles and international guidelines were hand searched to identify additional reports. All identified studies were screened for eligibility, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* [15]. As this systematic review focused on the management of sexual dysfunction due to CNS disorders, studies on patients with peripheral neuropathy or surgical disruption of the genital autonomic nerve supply were excluded as were studies on fertility issues. Data extraction was independently performed by three authors (M.L., S.M., G.L.) followed by crosschecking and clarification of any differences by the senior author (G.D.P.).

Results

The flow diagram of literature searches and results is shown in Fig. 1. We identified 302 records. In all, 256 reports were assessed for eligibility, with 31 articles finally included in this systematic review.

Men

The assessment of neurogenic erectile dysfunction (ED) is based on various mandatory steps. Overall the assessment criteria stemmed from data on patients with neurogenic ED

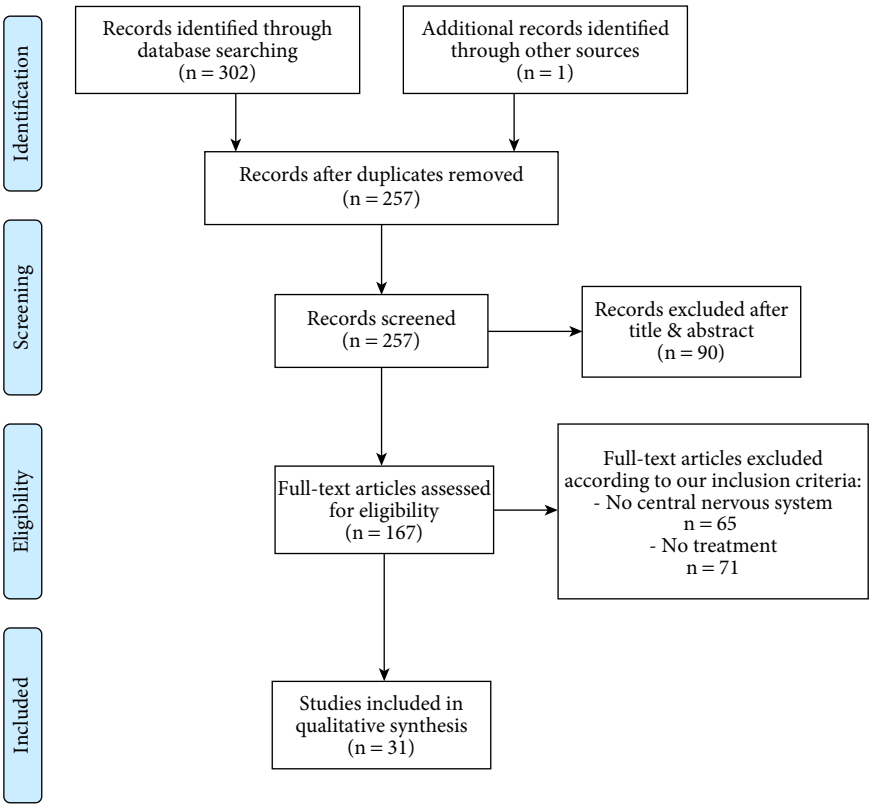

Fig. 1 PRISMA flow diagram.

treated with phosphodiesterase type 5 inhibitors (PDE5Is) [16–21].

History

Literature reported absolute exclusion criteria to better evaluate PDE5Is efficacy and avoid possible bias in clinical trials: patient's age (<18 years), concomitant neurological illness, neurological instability (no modification of previous neurological status in the past 6 months). Neurological patients were excluded if not in a stable partnership (relationship of <6 months) or were unable to attempt sexual intercourse at least once a week.

Moreover, current treatment with nitrates or nitric oxide donors, uncontrolled major psychiatric disorder or significant cardiovascular disease (stroke or myocardial infarction 6 months prior absolutely excluded the possibility of starting PDE5Is therapy) [16–21].

Conversely, the presence of co-morbidities such as diabetes or behavioural factors (e.g. chronic smoking or alcohol abuse) negatively influencing erectile function were not always considered absolute contraindications but they often required blood tests such as chemistry profile and glycated haemoglobin to determine whether using ED therapies would be possible [16,18,22,23].

General Assessment

Resting hypotension (systolic blood pressure <90 mmHg) or hypertension (systolic blood pressure >170 mmHg) were reported as exclusion criteria [16,22–24].

Uro-genital malformations and/or abnormalities, e.g. penile curvature or severe hypospadias, were reported as exclusion criteria for neurogenic ED treatment [22,23,25,26].

Neuro-physical Assessment

Safarinejad [20] reported neurophysiological studies, such as pudendal nerve cortical somatosensory evoked potentials (SEPs) and tibial nerve cortical SEPs before starting PDE5Is.

Men with spinal cord injury (SCI)

The American Spinal Injury Association (ASIA) Impairment Scale (AIS) was used to determine the level of lesion and their impairment grade: complete (AIS A) vs incomplete (AIS B–D) [16–20].

Through AIS, Khorrami et al. [19] defined two groups of lesions: the upper motoneurone (UMN) lesion referring to injuries above the thoracic (T) levels at or above T11 and lower MN (LMN) lesion with a level lower than T11.

Evaluation of erectile function

Some authors reported the presence of residual erectile function only in men with SCI, evaluating reflexive erection and/or psychological erection through the Erectile Assessment Score (EAS), which varies from 1 (no response) to 5 (full rigidity) [16,18,22,23].

Additionally, some authors performed intracavernosal injection (ICI) with prostaglandin E_1 (10–20 μg). Patients unable to obtain a valid erection were excluded from PDE5Is therapy because vascular disease was the main cause of their ED [17,21,24].

Men with MS

All men with MS treated with PDE5Is underwent standard neurological examinations using the Kurtzke Expanded Disability Status Scale (EDSS). A score >6 always indicated exclusion from PDE5Is treatment [21,24,27].

Outcome Measures for Neurogenic ED

Various outcome measures for evaluating the efficacy of neurogenic ED treatments were used. The most frequently used tool to specifically assess erectile function is the International Index of Erectile Function composed of 15 questions (IIEF-15) [16,21,24,27–30].

Laboratory Investigations

Before starting therapy, most authors performed blood sexual hormonal tests. Only patients with normal sexual hormonal profile levels were included [16,21–26].

PDE5Is Treatment

Men with SCI (Table 1)

The clinical efficacy of sildenafil (Viagra®), vardenafil (Levitra®), and tadalafil (Cialis®) is documented. More than 80% of patients reported trauma as the cause of their SCI [17–19,22,23,28]. UMN lesions, the preservation of residual erection with a score >2 on the EAS, and incomplete lesions (AIS A vs incomplete AIS B–D) represented positive prognostic factors for the success of PDE5Is therapy [22,25,29].

Furthermore, the medium- and long-term efficacy of sildenafil and tadalafil has also been documented in follow-ups of up to 10 years [16,22].

Significant statistical improvement ($P < 0.01$) on antegrade ejaculation using question 9 of the IIEF-15 was detected at the end of the clinical trials using tadalafil, vardenafil and sildenafil [25,29,31].

In studies comparing several ED treatments, Del Popolo et al. [17] showed that for patients with SCI tadalafil 10 mg was more effective at 12–24 h after dosing than sildenafil 50 mg.

Moemen et al. [26] evaluated the efficacy, safety and patient preference for different ED treatments. One 20-patient group

Table 1 PDE5i results for neurogenic ED in SCI patients.

	Reference (year)	Type of Trials			Study duration, weeks	Number of patients on PDE5Is (dose, mg)/total	IIEF-15 domains	SEP (1–5)	GEQ (1–2)	Other tools	*P*
		Multicentre	RCT	Control group							
Sildenafil											
	Ergin et al. [18] (2008)	Yes	Yes	Placebo	16	50 (50–100)/100	EF OS				*<0.05** *<0.01*
	Khorrami et al. [19] (2010)	No	Yes	Placebo	24	59 (25–100)/105				IIEF-5	*<0.05***
	Lombardi et al. [16] (2009)	No	No	N/A	480	37 (50–100)/37	EF, SS, OS				*<0.05*
	Moemen et al. [26] (2008)	No	No	N/A	4–8	60 (25–100)/60				IIEF-5	*<0.01*
	Soler et al. [31] (2007)	No	Yes	Tadalafil (10–20 mg) Vardenafil (10–20 mg)	≈40	57 (50–100)/90	EF, SS, OS, EJ, OF				*<0.05*
Tadalafil											
	Morgentaler et al. [30] (2006)	Yes	No	N/A	12	49 (10–20)/49	EF, OS, SS	SEP 1–5			*<0.01*
	Giuliano et al. [25] (2007)	Yes	Yes	Placebo	12	142 (10–20)/186	EF, EJ	SEP 2	GEQ 1,2		<0.01
	Lombardi et al. [22] (2009)	No	No	N/A	144	74 (10–20)/74	EF, OS,SS	SEP 2,3			*<0.01*
	Del Popolo et al. [17] (2004)	No	Yes	Sildenafil 50 mg	12	28 (10)/28		SEP 2,3			*<0.01*
Vardenafil											
	Giuliano et al. [28] (2006)	Yes	Yes	placebo	12	207 (5–20)/418	EF	SEP 2,3			*<0.01*
	Giuliano et al. [29] (2008)	Yes	Yes	placebo	12	207 (5–20)/418	EJ,OF				*<0.01*
	Kimoto et al. [23] (2006)	Yes	No	N/A	12	32 (10–20)/32	31% on 10 mg reached a mean EF > 26.9 at 4 weeks			N/A	N/A

*RCT, randomised controlled trial; N/A, not available; EF (1–5, 15), erectile function domain using questions 1 to 5 and 15; EJ (9), ejaculation frequency using question 9; SS (6–8), sexual satisfaction domain using questions 6 to 8; OF(10), orgasmic function using question 10; OS (13–14), overall satisfaction domain using questions 13 and 14; GEQ 1, global efficacy questions 1 and 2; SEP(1–5), sexual encounter profile questions 1 to 5; *Only for the 20 patients with incomplete lesion. **Only for patients with UMN lesion (37/45 using sildenafil vs 7/27 treated with placebo).*

was given ICI (10 μg prostaglandin E_1 or 0.5 mL Trimix) for 1 month and was then shifted to sildenafil. In all, 18 patients reached normal scores in the erectile domain of the IIEF questionnaire composed of five questions (IIEF-5) both with sildenafil and ICI vasoactive medication. However, 14 of 20 patients reported that they preferred sildenafil due to its easier administration. Another group of 20 patients used a vacuum device for 1 month, and subsequently sildenafil for 1 month. In all, 14 patients reached a normal erectile domain score with the vacuum device compared with 18 with sildenafil. None from this group was satisfied by the vacuum device therapy.

Finally, Soler et al. [31] in a randomised controlled trial comparing three different PDE5Is, showed that only the sildenafil group had a statistically significant improvement on the ejaculation and orgasmic domains of the IIEF-15. All three groups showed a significant amelioration on erectile function, satisfaction and overall satisfaction.

MS

Three sildenafil studies reported contradictory efficacy results for patients with MS with ED. Fowler et al. [27] showed an 89% improvement rate in erectile function of the patients selected. Lombardi et al. [21,22] using tadalafil (10 or 20 mg) confirmed a high percentage of erectile function enhancement, similar to the Fowler et al. study. In all, 70 of 92 patients (76.1%) who completed the 12-week treatment reached a normal score for the IIEF-15 erectile function domain. On the contrary, Safarinejad [20] did not find sildenafil improved erectile function at all compared with placebo.

Parkinson's disease

One study of Safarinejad et al. [24] was selected according to our criteria. In all, 116 patients in the sildenafil 100 mg group showed a significant increase in the IIEF erectile function score and in the percentage of 'Yes' responses to the Global Efficacy Questions 2 and 3 ($P < 0.001$) compared with 115 patients in the placebo group. A normal erectile function domain score (≥26) was achieved by 56.9% and 8.7% of the patients in the sildenafil and placebo groups, respectively ($P = 0.001$).

Side-Effects of PDE5Is

The most common side-effects reported in men with neurogenic ED using PDE5Is were headache and flushing. A low percentage of patients (<5%) discontinued treatment for severe adverse events (AEs) correlated to the drug assumption [16–21,24].

Other Treatments for Neurogenic ED

Drug therapy

Fampridine (also known by its chemical name of 4 aminopyridine, or 4-AP) is a specific drug used for neurogenic spasticity in patients with chronic and incomplete SCI or MS. One study evaluated the impact of this drug on erectile function as well. Two domains of the IIEF-15, erectile function ($P = 0.016$) and orgasmic function ($P = 0.032$), were significantly improved at the end of the 12-week treatment compared with placebo in only one (SCI-F301) of the two identical double-blind placebo-controlled studies including 185 male patients. In all, 19 patients (16.7%) discontinued because of severe AEs. The authors did not report data on previous treatments for neurogenic ED [32].

Strebel et al. [33] showed disappointing results with fixed dosages of sublingual apomorphine (3 mg). Only two of 22 patients were able to achieve valid sexual intercourse. In all, 11 patients of 22 presented side-effects, and two of them discontinued the treatment for intolerable AEs.

Pohanka et al. [34] reported that 14 patients with advanced Parkinson's disease and treated with a fixed dose of 3 mg of pergolide mesylate (Permax®) showed statistical improvement in all IIEF-15 domains compared with baseline up to the final 12-month follow-up. Concerning the IIEF-15 erectile function domain their mean score increased from 9.3 to 23.9 at the final follow-up ($P < 0.01$).

In a prospective randomised, double-blind trial comparing the effects of 3-months anastrazole plus testosterone (18 patients) vs testosterone plus placebo (18 patients) in hypogonadic epileptic men, Herzog et al. [35] found both groups significantly increased their scores ($P < 0.001$) on the IIEF-5.

Perineal electrostimulation

In a study by Shafik et al. [36], 18 patients with MS with neurogenic ED showed a substantial rise in intracavernosal pressure during repetitive percutaneous perineal electrostimulation lasting from 15 to 20 min ($P < 0.05$).

Neuromodulation

In two studies in which men with incomplete SCI were submitted to a monolateral sacral S3 electrode implant for their neurogenic LUTS (NLUTS) the evaluation of erectile function was assessed at baseline and in the follow-ups after permanent sacral neuromodulation (SNM) (Medtronic®, Minneapolis, MN, USA) at 3 months and subsequently every 6 months after permanent SNM using the IIEF-5. Scores ≥25%, compared with baseline, of the total IIEF-5 score indicated remarkable enhancement on erectile function, and those patients were considered 'responders'. An IIEF-5 score of ≥22 represents normal erectile function. Overall, 10 of 22 men with incomplete SCI reached and maintained a normal IIEF-5 score for >3 years at the final follow-up. However, four patients were contralaterally re-implanted on the S3 root during follow-up because they had lost clinical voiding and erectile function benefits [37,38].

On the contrary, 10 patients with complete lesions according to the AIS had bilaterally implanted sacral S3 lead during their shock phase to prevent neurogenic detrusor overactivity. Two patients reported subjective amelioration on erectile function at 6 and 24 months follow-ups, respectively [39].

Penile prosthesis

As for penile prosthesis, Zermann et al. [40] showed that sexual intercourse was possible for 77 of 92 patients with SCIs (83.7%) with a mean follow-up of ≈7 years for patients who had exclusively undergone penile prosthesis for ED. Several types of penile prosthesis were used. Only nine patients were included pre-sildenafil release and they were 'non-responders'. During follow-ups, 12 patients (16.3%) did not use the prosthesis for sexual intercourse. They complained about instability of the erect penis or symptoms related to the concord phenomenon.

Women

History

Women with a previous history of sexual dysfunction before their diagnosis of neurological illness were excluded for treatments [32,41–44].

Furthermore, a woman's neurological status had to be stable for ≥6 months before therapy. Only sexually active women were included [32,41–44].

Information regarding the correlation between the use of specific medication for their neurological disease and sexual response was requested: 'not related', 'partially related' and 'totally related' [44].

Specific Neurological Assessment

The AIS assessment provided inclusion/exclusion criteria or predictable factors for success on the basis of the level and degree of lesion. Women with the ability to perceive T11–L2 pinprick sensations may have psychogenic genital vasocongestion. Reflex lubrication and orgasm are more prevalent in women with SCI who had preserved the sacral reflex (S2–S5). For those with complete SCI of the sacral segment, arousal and orgasm may be evoked through stimulation of other erogenous zones above the level of lesions such as the breasts, lips, and ears [2,45].

Neurophysiological assessment using pudendal and tibial SEPs was reported by one author [42].

Specific Questionnaires for Assessing Primary Sexual Dysfunction

The tools most used for neurological females were the Female Sexual Function Index (FSFI) and the Sexual Function Questionnaire (SFQ) (Table 2).

Table 2 Results on neurogenic female sexual dysfunction.

Reference (year)	Neurological disease	Type of trial	Study duration, weeks	Treatment dose, mg	Number of patients treated/total included	Outcome measures	Domains	P
Dasgupta et al. [42] (2004)	MS	Cross over RCT placebo controlled / open label extension phase	28 / 36	Sildenafil 25–100	19 completed RCT phase 12/19 completed the extension phase	SFQ	Lubrication Orgasm	<0.05 <0.05
Cardenas et al. [32] (2014)	Incomplete SCI	Two Multicenter RCTs placebo controlled	12	Fampridine 25 twice daily	14/27 17/31	FSFI		>0.05 >0.05
Lombardi et al. [43] (2009)	Incomplete SCI	Open label Prospective study	≈96	Permanent SNM	4/9	FSFI	4 maintained up to the final follow-up total score of the FSFI ≥26.55 and a 50% of FSDS score	
Alexander et al. [41] (2011)	SCI	RCT placebo controlled	16	Sildenafil 25–100	67/129	SFQ		>0.05
Gil-Nagel et al. [44] (2005)	Epilepsy	Multicenter open label prospective trial	32	Lamotrigine 100–200/day	33/60 naïve group 27/60 shifted group	CSFQ	All domains Desire/frequency and desire/interest	<0.05 <0.05

RCT, randomised controlled trial; FSFI, female sexual function index questionnaire composed of 19 items in six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain as well as a total score); SFQ, sexual function questionnaire composed of 34 items in eight domains (arousal-sensation; arousal-lubrication; arousal-cognitive; desire, enjoyment, orgasm, pain and partner); CSFQ, changes in sexual functioning questionnaire including 14 items in five dimensions (desire/frequency, desire/interest, pleasure, arousal excitement and orgasm).

Specific Questionnaires for Secondary/Tertiary Sexual Dysfunction Conditions

A number of questionnaires or other objective evaluations (e.g. urodynamics, bladder diary) combined with specific questionnaires for primary sexual dysfunction (e.g. FSFI) were used to evaluate the degree of secondary factors influencing sexual function such as: bladder, bowel function, spasticity, and depression [32,37].

Laboratory Investigations

There is no recommended consensus about routine laboratory tests for neurological women with sexual dysfunction. Pregnancy was reported by some authors as an exclusion criterion for treatment [32,42,43].

Treatment Options for Neurogenic Primary Sexual Dysfunction in Females

There are no evidence-based therapeutic options to treat neurological women with sexual dysfunction.

Drug therapy

Dasgupta et al. [42] in a double-blind, randomised, placebo-controlled, crossover study investigated the positive effects on FSFI on women with MS of sildenafil starting with 50 mg and dose adjustment (25–100 mg) for tolerability or greater efficacy. In a double-blind placebo-controlled, flexible-dose study with a larger cohort of females with SCIs, Alexander et al. [41] showed a lack of clinically meaningful benefits with sildenafil.

Two phase III, multicentre, randomised, placebo-controlled clinical trials evaluating the use of fampridine sustained-release tablets to treat spasticity in females with incomplete chronic SCI did not show an amelioration in female sexual function [32].

Gil-Nagel et al. [44] in an open, prospective, multicentre study showed that females naïve to other anti-epileptic drugs who initiated lamotrigine for various seizure types gained more benefits in sexual function than women who switched to lamotrigine from previous anti-epileptic drugs inducing the hepatic P450 enzyme such as valproate, carbamazepine and phentyoin.

Neuromodulation

Female patients who underwent SNM for NLUTS were also evaluated for sexual dysfunction.

Lombardi et al. [43], in a 2-year follow-up after permanent SNM, reported that 36.5% of females with SCI and sexual dysfunction obtained positive effects on sexual response and showed a remarkable concomitant improvement through the Female Sexual Distress Scale (FSDS) questionnaire, which measures sexually related distress.

Discussion

Many individuals with neurological disorders have impaired sexual function that require various steps to manage challenges, starting with an accurate assessment of the disorder such as to tailor diagnostic investigations and treatments to each individual. Ideally, due to the complexity of sexual issues for neurological patients, management should be based on multidisciplinary teamwork starting at the onset of the neurological diagnosis and lasting for life. Scheduled follow-ups at rehabilitation centres or in neurological departments must comprehend sexuality issues. Therefore, cooperation among medical specialists and other health professionals is needed [10,46]. Although the PLISSIT (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) model, which has health professionals actively addressing primary, secondary, and tertiary factors, has been successfully applied only to patients with SCI, it could be useful for all neurological patients [2].

No data have been found about treatment of sexual dysfunction in spina bifida adults over recent decades. One possible reason may be the difficulty in evaluating their sexual dysfunction and its impact on their quality of life, due also in part to psychogenic issues. Adolescents with spina bifida cannot have proper knowledge of sexuality because they have never experienced it. Ideally an appropriate sex education starting in childhood and taking into account all aspects related to sexuality should be provided for their sexual health [47–49].

Neuro-physiological investigations are not mandatory for neurological patients before starting sexual dysfunction treatment, neither to determine the severity of ED in men, nor the type and degree of female sexual dysfunction. Moreover, their role as predictive factors for the success of ED and female sexual dysfunction therapies is controversial. A hypothesis, especially relevant for women, is that several neurophysiological tests do not examine certain aspects that may influence female sexual response such as marital satisfaction and marital communication, according to the Basson et al. [50] model.

For the evaluation of blood sexual hormones, most studies on males with neurogenic ED performed hormonal assessment before oral treatments at baseline in order to avoid ED related to sexual hormonal abnormalities [16,20–23,25,26].

It is well documented that neurological patients have higher risks of hormonal modifications (mainly low levels of testosterone) compared with the non-neurological population [51]. Checking the hormonal status may discriminate between possible therapies and help to decide appropriate treatment. In

women of reproductive age, a correlation between female sexual dysfunction and blood sexual hormonal status is not demonstrated. However, the interaction between the CNS and female sexual function hormones and their aetiological roles in sexual dysfunction is complex. A strategy that includes blood sexual hormonal assessment and subsequent hormonal replacement is still undefined [52,53]. Both testosterone and oestriol have been found to induce anti-inflammatory, as well as neuroprotective effects in MS [53]. Furthermore, oestrogen replacement probably benefits women with SCI more than it does non-neurological patients. In fact, oestrogens prevent osteoporosis, which is accelerated in the paralyzed and not charged areas [52,54].

Despite those potential benefits, there are some negative aspects to using hormonal therapies on neurological patients. For example, females with an absence or reduction of lower limb motility may have a high risk of thromboembolism. Again, the use of sexual hormones on females with catamenial epilepsy may increase the rate of seizures [1,4].

For specific neurogenic ED treatments, the existing body of evidence suggests that the PDE5Is sildenafil, vardenafil and tadalafil are first-line therapies for patients with SCI. However, no information has been reported to date on the efficacy/safety of the newer PDE5Is, avanafil and mirodenafil. Data on PDE5Is used on other patients with neurogenic ED are partial or missing. For male patients with Parkinson's disease and MS, the existing results are encouraging. For other central neurological diseases, such as MSA and epilepsy, data seems to suggest avoiding the use of PDE5Is as a first-line treatment for neurogenic ED due to possible severe AEs. Hussain et al. [55] showed that three of six patients with MSA had a severe blood pressure plunge 1 h after sildenafil was administered (systolic blood pressure <65 mmHg and diastolic blood pressure <55 mmHg). Instead, information is currently insufficient to speculate whether PDE5Is may prompt epileptic seizures in previous non-epileptic subjects, and whether they may increase ictal episodes in pharmacologically well-controlled seizure disorders [55–57]. However, the choice of anti-epileptic drug seems to be one cause of sexual dysfunction that is modifiable. Sexual dysfunction is related to anti-epileptic drugs that induce the hepatic P450 enzyme with a progressive increase of sex-hormone-binding-protein levels and consequently a decrease in free, bioavailable testosterone [58]. This may explain the improvement in epileptic hypogonadic men on sexual function treated with testosterone [35].

Similarly, women who had previously used anti-epileptic drugs inducing cytochrome P450 improved sexual function less than women who started lamotrigrine as first monotherapy [59,60].

International guidelines recommend ICI vasoactive drugs as a second-line treatment [2]. However, data on the efficacy of ICI vasoactive medications for neurogenic ED are lacking following the release of PDE5Is. Thus, no studies have been done that exclusively include PDE5I non-responders or offer different possible solutions as second-line treatment, alone or combined (vacuum device, testosterone, ICI plus PDE5Is, or PDE5Is plus testosterone).

In addition, there are no data on the daily use of PDE5Is as penile rehabilitation for patients with a CNS disorder, compared with those with a peripheral neurological disease, to favour the enhancement of angiogenesis and neurogenesis of corpora cavernosa function [61].

For specific treatments for primary female sexual dysfunction, data are poor and controversial. Particularly, sildenafil has been tested only on female patients with MS and SCI for possible benefits in arousal response, although these findings need to be confirmed with larger cohorts [41,42].

A common treatment for NLUTS for both genders is permanent SNM. The presence and impact of this therapy on sexual function has been evaluated by validated questionnaires at baseline and during follow-up after permanent SNM implantation in the medium- and long-term [43,52,56].

The objective assessment of sexual function in a treatment approved for NLUTS is a new strategy of evaluation. Although definitive SNM is not yet indicated for sexual dysfunction, an objective evaluation approach regarding sexual function should be recommended for all neurological patients [37,38,43,62,63]. The mechanism of SNM on sexual function is unknown, but potential direct mechanisms are possible. Positive findings in neurological females compared with non-neurological patients supported this thesis [43,63]. Only continual monitoring of patients who have undergone permanent SNM may clarify possible predictable and positive factors on sexual dysfunction, such as stimulation setting parameters [37,38,43,63].

A similar methodological approach was recently reported on, which evaluated the impact of fampridine (a drug mainly used for lower limb motility) on sexuality, using validated questionnaires for both genders [32]. At the same time, during primary treatment (such as PDE5Is) for sexual dysfunction, objective assessment should also be done to evaluate impact on secondary conditions that may interfere with therapeutic success [64]. This holistic methodology may help to select an appropriate and patient-tailored treatment. Based on the multiple factors that influence neurogenic sexual dysfunction, creating specific questionnaires for these patients is necessary.

Conclusions

Although sexual dysfunction is a major burden for patients with CNS disorders, high-level evidence is only available on PDE5Is that treat ED; well-designed prospective studies are urgently needed for both genders.

Conflicts of Interest

G.D.P. consultant for: Hollister, Ipsen, Allergan, Wellspect, Apogepha; Honorary Speaker: Astellas, Allergan, Sigma Tau; Trials: Pfizer, Allergan, Ipsen, Recordati, Astellas.

All other author have nothing to disclose.

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Abbreviations: AE, adverse event; ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale; EAS, Erectile Assessment Score; ED, erectile dysfunction; FSDS, Female Sexual Distress Scale (questionnaire); FSFI, Female Sexual Function Index; ICI, intracavernosal injection; IIEF(-5)(-15), International Index of Erectile Function questionnaire (composed of five questions) (composed of 15 questions); (L)(U)MN, (lower) (upper) motoneurone; MS, multiple sclerosis; MSA, multiple system atrophy; NLUTS, neurogenic LUTS; PDE5I, phosphodiesterase type 5 inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCI, spinal cord injury; SEP, somatosensory evoked potential; SFQ, Sexual Function Questionnaire; SNM, sacral neuromodulation.