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Efficacy of Neuromodulation Interventions for the Treatment of Sexual Dysfunction: A Systematic Review

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ABSTRACT

Objectives: The primary aim of this review was to analyze the literature for the efficacy of neuromodulation interventions in treating both male and female sexual dysfunction.

Materials and Methods: Studies were identified from PubMed, Scopus, PsychINFO, CINAHL, and Cochrane. Results were synthesized qualitatively without pooling owing to the heterogeneous nature of outcome assessments.

Results: Overall findings from studies generally supported that neuromodulation interventions were associated with improvement in sexual function. Specific domains that improved in male patients included erectile function, desire, and satisfaction, whereas desire, arousal, orgasm, lubrication, quality of "sex life," intercourse capability, and dyspareunia improved in female patients. Male ejaculation, orgasm, and intercourse capability were the only domains that continued to decline after the use of neuromodulation interventions, although this was only reported in one study.

Conclusion: Our review suggests that there may be promise and potential utility of neuromodulation in improving sexual dysfunction; however, further research is needed.

Keywords: Neuromodulation, peripheral nerve stimulation, review, sexual dysfunction, spinal cord stimulation

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Sexual dysfunction is defined as significant distress that is caused by repeated problems related to the experience, response, and pleasure from performing sex.[1] The types of sexual dysfunction can be separated into sexual desire disorders, sexual arousal disorders, orgasmic disorders, and genital pain disorders.[2] Sexual desire disorder consists of hypoactive sexual desire disorder.[2,3] Sexual arousal disorders include erectile dysfunction (ED) and persistent genital arousal.[2,4] Orgasmic disorders include premature ejaculation, anejaculation, and female orgasmic disorder.[2,4] Genital pain disorders include dyspareunia and vaginismus.[2]

Sexual dysfunction can negatively impact patient quality of life and emotional functioning. Primarily, sex life is negatively impacted owing to both emotional and physical discomfort, in addition to lack of functionality.[5] Decreased sexual function is related to poor marital satisfaction.[6] In addition, a couple's capability of having children is threatened because of reduced sexual intercourse. Sexual dysfunction not only impacts a person's sex life but also places people at a higher risk for depression and other mood disorders.[7]

An important distinction to make is that sexual dysfunction from neurological conditions is pathologically different from those associated with nonneurological conditions. This is important because patients with neurological conditions including traumatic brain injury, Parkinson disease, multiple sclerosis, spinal cord injury, and diabetic neuropathy experience an increased prevalence of sexual dysfunction.[8] Neurological disorders can alter the processing of sexual stimuli through the disruption of long spinal tracts between the cortex and the sacral nerve roots or the pelvic autonomic nerves.[9] Although etiologies may be distinct, we query whether neuromodulation may potentially benefit sexual dysfunction regardless of the etiology.

Many treatments for sexual dysfunction, including neuromodulation, do not differentiate between neurologic and nonneurologic causes. The typical management of sexual dysfunction involves psychosexual counseling therapy consisting of general sex therapy, systematic desensitization, and directed masturbation.[2,3,10–14] Psychosexual counseling is the only treatment option available for many disorder types. For other disorders, treatment options may vary. ED is the most prevalent sexual disorder and has several approved treatments.[2] Pharmaceutical treatment includes phosphodiesterase-5 inhibitor medications (sildenafil, tadalafil, or vardenafil). Alternatively, patients may receive penile injections (alprostadil).[12] Other treatments include vacuum constriction devices, intraurethral prostaglandin

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suppositories, and penile prosthesis.[12] For orgasmic disorders such as premature ejaculation, pharmaceutical options include serotonin reuptake inhibitors, tricyclic antidepressants, or topical lidocaine.[10] Anejaculation can be managed by stopping any intake of alpha-blockers and antidepressants.[11] The use of penile vibratory stimulation is another treatment option.[11] If retrieval of semen is desired in patients who experience anejaculation, treatment modalities include artificial insemination, electroejaculation, and other surgical methods.[11] Genital pain disorders are treated with physiotherapy that includes pelvic floor exercises.[14] Vaginismus also can be treated with pelvic floor botulinum toxin injections, although physiotherapy may be more effective.[15] Alternatively, pelvic pain can be managed with application of lidocaine or administration of tricyclic antidepressants or gabapentinoids.[14] Hormone replacement therapy (HRT) is a common treatment method for female sexual dysfunction (FSD). Estrogen replacement therapy is a specific type of HRT used that improves pain, lubrication, arousal, and orgasm symptoms.[16,17] In addition to systemic therapies, estrogen can be applied locally in the form of creams (eg, topical vaginal estrogen) to reduce vaginal atrophy.[16] Vaginal dilator therapy is an alternative treatment option for managing vaginal atrophy.[18] Testosterone supplementation through patches or gels also has been used for the treatment of FSDs. Testosterone supplementation may improve frequency of sexual activity, pleasure, and fantasy.[16,18] Recently, advances have been made in vaginal laser treatment that allows for increased vascularity and production of collagen, although this treatment is not approved by the Food and Drug Administration.[18] Patients with sexual dysfunction and underlying gynecological conditions (eg, pelvic organ prolapse) may require a multidisciplinary approach that involves treating the gynecological conditions first.[19]

Neuromodulation interventions including spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS) are emerging therapies that can be used in lieu of opioids, other pharmacologic agents, and other interventional options. Currently, SCS is indicated for failed back surgery syndrome, refractory angina pectoris, peripheral arterial disease, complex regional pain syndrome, painful diabetic neuropathy, and nonsurgical low back pain.[20] For urinary and bowel dysfunction, sacral nerve stimulation is a common neuromodulation intervention. Sacral nerve stimulation is currently indicated for urinary retention, urinary frequency, urge incontinence, and fecal incontinence.[21] Although neuromodulation interventions are an uncommon indication, patients also may experience a positive improvement in sexual function with use of SCS and other neuromodulation interventions.[22]

There are significant knowledge gaps regarding the efficacy of neuromodulation interventions for sexual dysfunction. In the neuromodulation literature, a major knowledge gap exists on the regain or recovery of neurological function after the application of SCS or PNS. It is common for disorders of sexual dysfunction also to comprise neurological deficits within the genitourinary system, and we query whether neuromodulation interventions may be associated with improvements in neurological function. The purpose of this systematic review is to analyze all available literature that reports the use of SCS, PNS, or other neuromodulation interventions in the treatment of sexual dysfunction. The target population is anyone experiencing sexual dysfunction, regardless of etiology. The primary outcome of this review is to determine the efficacy of neuromodulation interventions in treating sexual dysfunction, as indicated on specific objective sexual function questionnaires.

MATERIALS AND METHODS

Search Strategy

This study was registered a priori under The International Prospective Register of Systematic Reviews (CRD42021285375).[23] We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Supplementary Data Table S1).[24] As such, we broadly searched all articles from different electronic data bases from inception of data base to May 2022, including PubMed, Scopus, PsycINFO, CINAHL, and Cochrane. We also hand-searched reference lists of identified publications. Broad MeSH terms and Boolean operators were selected for each data base search, including terms and synonyms for spinal cord stimulation, peripheral nerve stimulation, dorsal root ganglion stimulation, spinal neuromodulation, sacral nerve stimulation, tibial nerve stimulation, posterior tibial nerve stimulation, saphenous nerve stimulation, peroneal nerve stimulation, sural nerve stimulation, sciatic nerve stimulation, femoral nerve stimulation, sexual function, sexual dysfunction, erection, orgasm, and pain. This search strategy was verified by a senior academic librarian (Mary Hitchcock). The specific syntax and number of results for each data base are presented in Supplementary Data Table S2.

Study Selection

Included studies abided to the following criteria: any study design that involved patients receiving neuromodulation (dorsal column spinal cord stimulator, dorsal root ganglion stimulator, or peripheral nerve stimulator targeting tibial nerve, sacral nerve, saphenous nerve, peroneal nerve, sural nerve, sciatic nerve, or femoral nerve) and included patient-reported outcomes of sexual function (eg, orgasm, erection, desire, lubrication, satisfaction). The patient-reported outcomes of sexual function can be quantitative (eg, improvement of Female Sexual Dysfunction Index [FSFI] score) or qualitative (eg, ability to maintain erection).

The exclusion criteria consisted of nonpeer reviewed studies, review or meta-analysis articles, nonhuman studies, unpublished clinical trials, and articles in a foreign language. Two authors (Max Y. Jin and Ryan S. D'Souza) independently selected abstracts along with full-text articles from the above-listed data bases, whereas a third author (Alaa A. Abd-Elsayed) resolved any discrepancies.

Data Extraction

The data extracted were 1) study characteristics (indication, type of stimulation and location, study design, primary outcome assessment, secondary outcome assessment); 2) participant demographics (sample size, average age, duration of sexual dysfunction, type of neurological impairment); and 3) primary and secondary outcomes after neuromodulation intervention**.** To evaluate the magnitude of effect, authors extracted numerical data and calculated the mean difference for studies that provided continuous data on sexual dysfunction.

The primary outcome of interest was changes in overall sexual function after neuromodulation intervention, based on the evaluation of specific sexual function domains including erectile function, ejaculation, orgasm, intercourse capability, desire, arousal, lubrication, quality of "sex life," and dyspareunia. The secondary outcome of interest was changes in urinary or bowel symptoms. Outcomes were required to be at least six months after neuromodulation intervention. For each included study, two authors (Max Y. Jin and Ryan S. D'Souza) independently extracted all

relevant data with a third author (Alaa A. Abd-Elsayed) arbitrating any disputes.

Assessment of Risk of Bias

The risk of bias was assessed using the Newcastle-Ottawa scale (NOS) and the Cochrane risk of bias assessment tool.[25,26] The NOS is a validated tool for observational studies,[26] and the strategy has been used to analyze observational studies in previous systematic reviews.[27,28] The NOS is only appropriate for observational studies (case-control or cohort studies), which comprised most of the included studies in our systematic review. It is not appropriate for randomized controlled trials (RCTs). For this reason, the Cochrane risk of bias assessment tool also was used for RCTs included in this review. Case reports and case series were excluded from any bias assessment. For the NOS, biases were assessed for three domains: Selection, Comparability, and Exposure/Outcome. Assessment of selection bias was completed by evaluating the representativeness of the sexual dysfunction cohort, selection of the sexually functioning cohort, ascertainment of exposure, and demonstration that the outcomes of interest were not present at the start of the study. Assessment of comparability bias was completed by evaluating the study designs and analyses, checking specifically whether they control for age, sex, sexual partner status, and other variables. Outcome bias was assessed by evaluating the outcome assessment in addition to the length and adequacy of follow-up. Each specific evaluation item can be assigned a maximum of one star. A maximum of two stars can be given for the comparability domain. Studies with more stars assigned in each domain were identified as having lower risk for bias for those respective domains. The Cochrane risk of bias assessment tool assessed biases for the domains of Selection, Performance, Detection, Attrition, Reporting, and other biases. Assessment of selection bias was completed by evaluating the generation of a random sequence and concealment of allocation. Assessment of performance bias was completed by evaluating the blinding of participants and personnel. Assessment of detection bias was completed by evaluating the blinding of outcome assessment. Assessment of attrition bias was completed by evaluating the completeness of outcome data. Lastly, assessment of reporting bias was completed by evaluating whether there was selective reporting. Each domain was assigned a grade of low risk, high risk, or unclear risk. For each included study, two authors (Max Y. Jin and Ryan S. D'Souza) independently assessed for risk of bias, with a third author (Alaa A. Abd-Elsayed) arbitrating any disputes.

Statistical Analysis

For studies that measured outcomes numerically (eg, FSFI), the authors abstracted preoperative and postoperative outcome scores (mean and standard deviation). From these abstracted data, an effective measure was calculated by deriving a mean difference value with a 95% confidence interval for each individual study. The calculation was computed using Review Manager software version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Search Results

The search strategy identified 1858 citations (Fig. 1). After independent and duplicate screening, 75 full-text studies were evaluated, and 30 studies[29–58] were selected that met the full eligibility criteria. The 30 selected studies consisted of 1232 patients (340 men and 892 women). Of included studies, 22 studies used sacral nerve stimulation[29–37,39–43,46–49,55–58]; five studies used tibial nerve PNS[50–54]; and three studies used dorsal column SCS.[38,44,45] No relevant studies were identified using saphenous nerve stimulation, peroneal nerve stimulation, sural nerve stimulation, sciatic nerve stimulation, femoral nerve stimulation, or dorsal root ganglion stimulation. Two included studies selected a control cohort, with one study[53] selecting a sham stimulation (needle placement stimulation without nerve stimulation) group and another study[58] selecting a conventional drug (onabotulinumtoxinA) injection group. No control cohort was selected in the remaining studies (these were longitudinal studies comparing postintervention outcomes with baseline outcomes). Study characteristics and patient demographics are outlined in Table 1 and Table 2, respectively.

Bias Assessment

The risk of bias of observational studies is summarized in Table 3. Six months was selected as an adequate follow-up period, whereas 95% of total participants followed up at the primary endpoint of study was deemed as an adequate follow-up rate. None of the observational studies selected a control cohort; thus, no bias assessment was completed in the comparability domain. In addition, studies evaluated for selection bias could only be given a maximum of three stars because no participants were selected from the nonexposed cohort. Most of the studies demonstrated low risk for selection bias. Three studies showed medium risk owing to selection of the exposed cohort from a specific group (overactive bladder[52]), written self-reported ascertainment of exposure,[32] or no ascertainment of exposure.[44] Two studies[40,41] showed high risk owing to no ascertainment of exposure and no report that the primary endpoints were absent at the start of the study. Nineteen studies demonstrated bias risk through self-reported assessment of outcome,[38,40,41,57] inadequate follow-up period,[31–33,36,37,41,46,47,50,54] or inadequate follow-up of cohorts.[29–31,36,43,46,48,50,54] The bias of two included RCTs[53,58] assessed using the Cochrane risk of bias assessment tool is summarized in Figure 2. Both studies demonstrated low risk of detection bias and other bias. One study[53] also demonstrated low risk for bias for all other domains except reporting bias, which was unclear. The other RCT[58] demonstrated low risk for reporting bias, high risk for performance and attrition bias, and unclear risk for the remaining domains.

Effects of Intervention

Erectile Function

The impact of neuromodulation on erectile function was evaluated across eight studies with a total of 295 patients.[34,40,41,43,46,48,53,57] Two studies used a retrospective observational study design[34,48]; five used a prospective observational study design[40,41,43,46,57]; and one used an RCT design.[53] In two studies that assessed the ability to maintain an erection with sacral nerve stimulation, 43 of 47 patients reported improvement in ability to maintain erection.[40,41] In another study using sacral nerve stimulation, the number of patients experiencing ED declined from nine to two.[57] The index of erectile function (IIEF-5) score was assessed for 66 patients across three studies[43,46,48] who underwent sacral nerve stimulation and in one study[53] of 16 patients who underwent tibial nerve PNS. Lombardi et al[43] separated results for patients with neurogenic and idiopathic dysfunction, and reported a median increase in IIEF-5 scores for both groups. In the two other

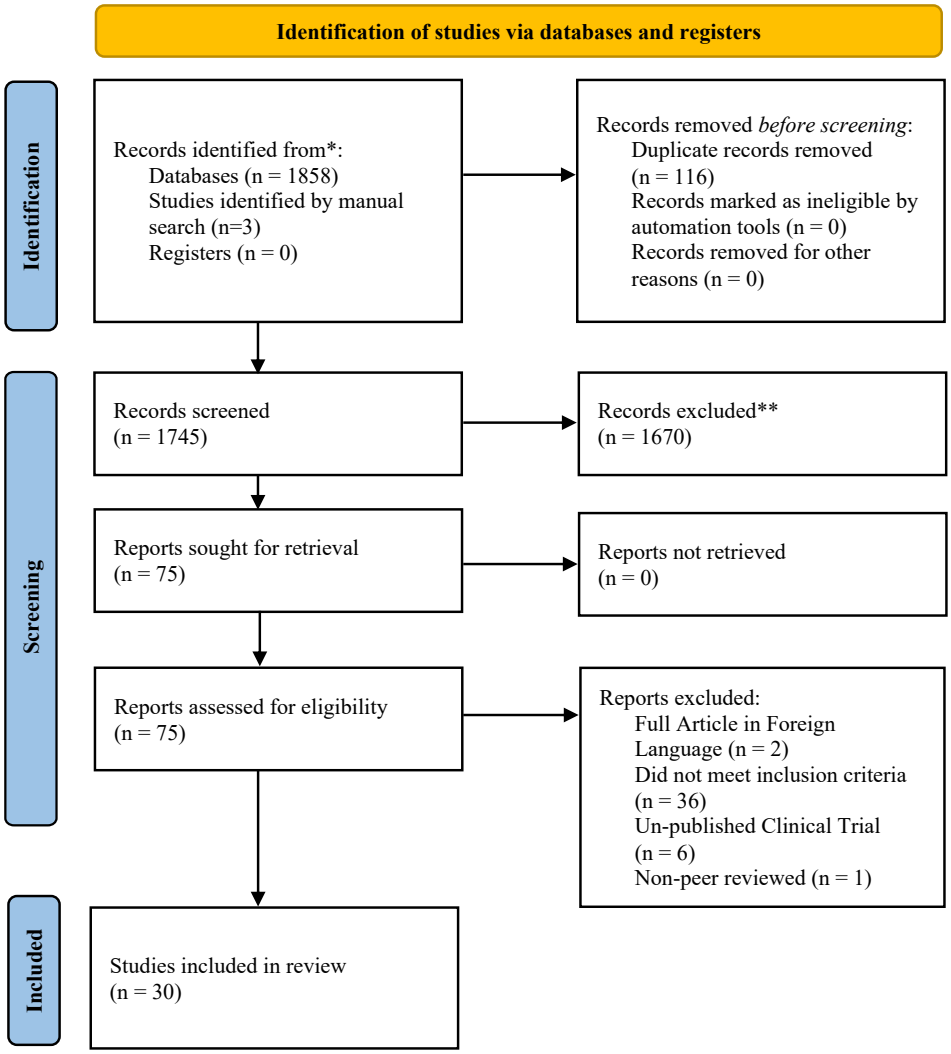

Figure 1. Flow chart of study selection and inclusion process. *Consider, if feasible to do so, reporting the number of records identified from each data base or register searched (rather than the total number across all data bases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. Source: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/. [Color figure can be viewed at www.neuromodulationjournal.org]

studies using sacral nerve stimulation, an overall increase in IIEF-5 scores also was found.[46,48] Marinello et al[53] used a tibial nerve PNS and found an overall decrease in IIEF-5 scores. In another study of 154 patients that used a questionnaire, it was found that patients had an overall decreased capability of erection, regardless of whether sacral nerve stimulation was used.[34]

Ejaculation, Orgasm, Intercourse Capability, Desire, and Satisfaction in Men

The effect of neuromodulation interventions on ejaculation, orgasm, and intercourse capability in men was evaluated in one study that had 154 patients.[34] This retrospective observational study found that the overall capability of all three domains decreased after implantation of the sacral nerve stimulator (ie, the sacral nerve stimulator worsened outcomes).[34] In another prospective observational study of 45 patients who underwent tibial nerve PNS, it was reported that overall desire and satisfaction increased.[54] Results pertaining to male sexual dysfunction are summarized in Table 4.

Desire and Arousal in Women

Data from 16 studies[29,30,33,35–37,39,46–49,52,54–56,58] of 639 total patients were used to assess changes in desire and arousal after neuromodulation interventions. Of the 13 studies[29,30,33,35–37,39,46–49,55] that used the FSFI to report changes in sexual function, 12 used a sacral nerve stimulator, whereas one study[52] used a tibial nerve stimulator. Of these 13 studies ($n = 388$), ten studies reported an improvement in desire ($n = 310$),[29,30,33,36,37,46,47,49,52,55] and nine studies reported an improvement in arousal ($n = 176$).[30,33,35,37,39,46,49,52,55] Using the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, Andy et al[58] found no significant changes in desire or arousal in 174 patients who underwent sacral nerve stimulation. Van Balken et al[54] used the Nine Questions Regarding Sexual Functioning Questionnaire (NSF-9) and found overall improvements in 76 patients who underwent tibial nerve PNS. In a case report ($n = 1$) by Jones et al,[56] it was found that the patient undergoing sacral nerve stimulation for treatment of persistent genital arousal experienced improvement in symptoms.

Table 1. Study Characteristics.

Study	Indication	Type of stimulation and location	Study design	Primary outcome assessment	Secondary outcome assessment
van der Aa et al[40]	Bladder function	Sacral nerve stimulation (S2-S3)	Prospective observational	Unspecified	Unspecified
van der Aa et al[41]	Bladder emptying, with defection and erectile function	Sacral nerve stimulation (S2-S5)	Prospective observational	Unspecified	Unspecified
Whiteside et al[45]	Vulvar pain	Dorsal column spinal cord stimulation (T10)	Case report	Unspecified	Unspecified
Jarrett et al[32]	Fecal incontinence with sexual relations	Sacral nerve stimulation (S3)	Survey	Sex Life Questionnaire	Unspecified
Meloy and Southern[38]	Neurally augmented sexual function (NASF)	Dorsal column spinal cord stimulation (varied from T10 to L3)	Prospective observational	Unspecified	None
van Balken et al[54]	Sexual function	Tibial nerve PNS (3 to 4 cm cephalad to the medial malleolus)	Prospective observational	NSF-9	I-QOL, SF-36, McGill Pain Questionnaire
Pauls et al[36]	Urinary symptoms and sexual function	Sacral nerve stimulation (S3)	Prospective observational	FSFI	Unspecified
Lombardi et al[43]	Erectile function	Sacral nerve stimulation (S3)	Prospective observational	IIEF-5	Unspecified
Lombardi et al[30]	Lower urinary tract symptoms with sexual function	Sacral nerve stimulation (S3)	Prospective observational	FSFI, FSDS	Unspecified
Zabihi et al[35]	Voiding dysfunction and sexual function	Sacral nerve stimulation (S2-S4)	Prospective observational	FSFI	Unspecified
Ingber et al[39]	Overactive/painful bladder syndrome with sexual function	Sacral nerve stimulation (S3)	Prospective observational	FSFI	IC-SIPI
Marcelissen et al[42]	Chronic pelvic pain	Sacral nerve stimulation (S3)	Case report	VAS	Voiding diary
Gill et al[37]	Refractory overactive bladder with sexual function	Sacral nerve stimulation (S3-S4)	Prospective observational	FSHQ, FSFI	PGI-S, HSI, UDI-6, IIQ-7
Signorello et al[55]	Sexual function, clinical outcome, and quality of life with overactive bladder	Sacral nerve stimulation (S3)	Prospective observational	FSFI	I-QOL, SF-36
Jadav et al[31]	Non-bowel related symptomatology	Sacral nerve stimulation (S3)	Prospective observational	ePAQ-PF	ePAQ-PF
Yih et al[29]	Urinary/bowel disorder with sexual dysfunction	Sacral nerve stimulation (S3)	Prospective observational	FSFI	ICSI-PI
Banakhar et al[47]	Female sexual function and quality of life	Sacral nerve stimulation (S3)	Prospective observational	FSFI	UDI-6, SF-36
Elkattah et al[51]	Clitoral pain	Tibial nerve PNS (location NR)	Case series	Unspecified	Voiding diary
Parnell et al[33]	Sexual function and pudendal nerve function with overreactive bladder	Sacral nerve stimulation (S3)	Prospective observational	FSFI, PISQ-12	PNTML, PFDI-20, PFIQ-7
Jones et al[56]	Persistent genital arousal	Sacral nerve stimulation (S3)	Case report	Unspecified	Unspecified
Kelly et al[50]	Global pelvic floor function	Tibial nerve PNS (at presence of motor or sensory response)	Prospective observational	ePAQ-PF	ePAQ-PF
Musco et al[52]	Overactive bladder with sexual dysfunction	Tibial nerve PNS (3 to 5 cm cephalad to the medial malleolus)	Prospective observational	FSFI	OAB-q SF
Zaer et al[34]	Neurogenic bladder and sexual dysfunction	Sacral nerve stimulation (S2-S4)	Retrospective observational	Questionnaire	Questionnaire

(Continued)

Table 1. *Continued*

Study	Indication	Type of stimulation and location	Study design	Primary outcome assessment	Secondary outcome assessment
Andy et al[58]	Sexual function and fecal incontinence with urgency urine incontinence	Sacral nerve stimulation (Location NR)	Randomized controlled trial	PISQ-12, PISQ-IR	St Mark's (Vaizey) fecal incontinence score, PISQ-12, PISQ-IR
Darrow et al[44]	Volitional movement and autonomic function with cardiovascular, sexual, bowel and bladder function	Dorsal column spinal cord stimulation (T12)	Case series	Unspecified	NBDS, NBSS, Forward and Backward Digit Span Test, Stroop Test, Controlled Oral Word Association Test
de Oliveira et al[48]	Sexual function	Sacral nerve stimulation (S3)	Retrospective observational	IIEF-5, FSFI	Unspecified
Zoorob et al[49]	Persistent genital arousal	Sacral nerve stimulation (S3)	Case Report	FSFI	Unspecified
Banakhar and Youness[46]	Male and female sexual function	Sacral nerve stimulation (S3)	Prospective observational	IIEF-5, FSFI	Unspecified
Ismail and Abdullhussein[57]	Urinary and fecal incontinence	Sacral nerve stimulation (S3)	Prospective observational	Unspecified	Voiding diary
Marinello et al[53]	Bowel disorders	Tibial nerve PNS (4 cm cephalad to the medial malleolus)	Randomized controlled trial	IIEF-5, FSFI	LARS score, St Mark's fecal incontinence score, QLQ-C30

FSHQ, Female sexual health questionnaire; HSI, Hunskaar Severity Index; I-QOL, Incontinence Quality of Life Questionnaire; IC-SIPI, Interstitial Cystitis Symptom and Problem Index; ICSI-PI, Interstitial Cystitis Symptom Index and Problem Indices; IIQ-7, Incontinence Impact Questionnaire; LARS score, Lower Anterior Resection Syndrome Score; NBDS, Neurogenic Bowel Dysfunction Score; NBSS, Neurogenic Bladder Symptom Scale; OAB-q SF, Overactive Bladder short-form questionnaire; QLQ-C30, Quality of Life Questionnaire; PFIQ-7, Pelvic Floor Impact Questionnaire Short Form; PGI-S, Patient global impression of severity; PISQ-12, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short form; PISQ-IR, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire; SF-36, Short-Form Health Survey; UDI-6, Urinary Distress Inventory; VAS, Visual Analogue Scale.

Orgasm and Lubrication in Women

The impact of neuromodulation on orgasm and lubrication in women was evaluated across 17 studies with a total of 705 patients. Of the 17 studies, 14 used a sacral nerve stimulator[29,30,33–37,39,46–49,55,58]; two used a dorsal column spinal cord stimulator[38,44]; and one used a tibial nerve stimulator.[52] All 17 studies reported outcomes related to orgasmic function, whereas 14 of the studies reported outcomes related to lubrication (n = 399).[29,30,33,35–39,46–49,52,55] Thirteen studies used the FSFI to report changes in sexual function. Of the 13 studies (n = 388), ten studies reported improvements in FSFI scores in the domains of orgasm (n = 338)[29,30,33,35,36,39,46,47,49,52] and lubrication (n = 190).[30,33,35–37,39,48,49,52,55] In the study by Meloy et al,[38] it was found that four of five patients with secondary anorgasmia experienced the return of orgasms with the implantation of a dorsal column spinal cord stimulator, and ten of 11 patients thought the stimulation was successful, with improvements in lubrication. Darrow et al[44] reported that one patient experienced no improvement of sexual function with dorsal column SCS, whereas another patient experienced the ability to have orgasms for the first time since spinal cord injury. In a questionnaire sent by Zaer et al,[34] it was found that in a pool of 130 patients, there was no significant change in capability of orgasm after implantation of a sacral nerve stimulator. Andy et al[58] found no significant changes with orgasmic ability in 174 patients who underwent sacral nerve stimulation.

Quality of "Sex Life" and Intercourse Capability in Women

Quality of "sex life" was assessed across 17 studies of 563 patients, with 14 studies using sacral nerve stimulation (n = 368)[29–33,35–37,39,46–49,55] and three studies using tibial nerve PNS (n = 157).[50,52,54] Fifteen of the 17 (n = 525)[29–33,35–37,39,46,47,50,52,54,55] studies found that there was an overall improvement in quality of "sex life." Reasons for this improvement were attributed to less incontinence,[33,37] decreased urgency,[32] fewer urinary and bowel symptoms,[31] and overall less distress.[30] Eleven of the studies demonstrated improvements in the quality of sex life through changes in the FSFI-satisfaction domain scores (n = 350),[29,30,33,35–37,39,46,49,52,55] whereas two other studies showed improvements through changes in the electronic Personnel Assessment Questionnaire–Pelvic Floor (ePAQ-PF) scores (n = 90).[31,50] One of the studies[43] that used the FSFI also showed improvements in quality of sex life through changes in the Female Sexual Distress Score (FSDS) (n = 17). The remaining two studies assessed quality of sex life using questionnaires (Sex Life Questionnaire[32] and NSF-9[54]), with Jarrett et al reporting improvement in seven of nine patients and van Balken et al finding overall improvements in satisfaction (n = 76). Intercourse capability was measured across 15 studies of 406 patients, with 12 studies using sacral nerve stimulation,[29,30,33,35–37,39,46–49,55] two studies using tibial nerve PNS,[52,53] and one study using dorsal column SCS.[38] Fourteen of the 15 studies found improved intercourse capability, with 13 studies demonstrating improved overall FSFI scores (n = 395)[29,30,33,35–37,39,46–49,52,55] and one study[34] demonstrating improvements in another questionnaire (n = 11). Marinello et al[53] used the FSFI and found an overall decrease in overall intercourse capability (n = 7).

Dyspareunia

Responses applicable to dyspareunia were found in 482 patients across 18 studies.[29–31,33,35–37,39,42,45–52,55] In 13 studies that used

Table 2. Participant Demographics of Included Studies.

Study	Sample size	Average age of participants	Duration of sexual dysfunction	Type of neurological impairment
van der Aa et al[40]	17 patients; 3 women, 14 men	37.2 years	Unspecified	Complete lesion of spinal cord (n = 17)
van der Aa et al[41]	38 patients; 5 women, 33 men	35.0 years	Unspecified	Complete lesion of spinal cord (n = 38)
Whiteside et al[45]	1 woman	21 years	3 years	Bilateral vulvar burning and tenderness (n = 1)
Jarrett et al[32]	16 women; 9 with sexual dysfunction	56 years	Unspecified	Bowel symptoms (n = 16)
Meloy and Southern[38]	11 women	32–60 years (no average reported)	Unspecified	None
van Balken et al[54]	121 patients; 76 women, 45 men	53.6 years	Unspecified	Overactive bladder (n = 83); chronic pelvic pain (n = 23); nonobstructive retention (n = 15)
Pauls et al[36]	11 women; 7 sexually active	50 years	Unspecified	Urgency frequency (n = 5); urge incontinence (n = 6)
Lombardi et al[43]	54 men; 52 sexually active	42.8 years	Unspecified	Spinal cord injury (n = 6); myelitis (n = 3); multiple sclerosis (n = 1); disk herniation (n = 2); peripheral polyneuropathy (n = 2)
Lombardi et al[30]	31 women; 17 with sexual dysfunction	37.6 years	Minimum of 1 year	Incomplete spinal cord injury (n = 5); myelitis (n = 3); multiple sclerosis (n = 3); intervertebral disk prolapse (n = 2); peripheral polyneuropathy (n = 4)
Zabihi et al[35]	36 women	49.5 years	Unspecified	Pelvic pain (n = 21); voiding dysfunction (n = 15)
Ingber et al[39]	105 women; 27 sexually active	50 years	Unspecified	Overactive bladder (n = 15); urgency, frequency, and pelvic pain (n = 14)
Marcelissen et al[42]	1 woman	51 years	Unspecified	Lower urinary tract dysfunction and clitoral pain (n = 1)
Gill et al[37]	33 women; 19 sexually active	58.5 years	Unspecified	Genital atrophy (n = 3); vaginal prolapse (n = 1)
Signorello et al[55]	16 women	62 years	Unspecified	Neurogenic bladder (n = 6)
Jadav et al[31]	43 women; 30 with sexual dysfunction	56.5 years	Unspecified	Vaginal prolapse (n = 21); urinary symptoms (n = 43); vaginal pain and sensation (n = 29)
Yih et al[29]	167 women	53.7 years	Unspecified	Interstitial cystitis/painful bladder syndrome (n = 48); overactive bladder (n = 106); pelvic pain (n = 1); urinary retention (n = 11)
Banakhar et al[47]	33 women; 23 sexually active	51 years	Unspecified	Overactive bladder (n = 19); frequency-urgency syndrome (n = 2); nonobstructive urine retention (n = 2)
Elkattah et al[51]	2 women	58.5 years	> 10 months	Urinary incontinence and clitoral pain (n = 2); fecal incontinence (n = 1); dyspareunia (n = 1)
Parnell et al[33]	31 women	67.4 years	Unspecified	Overactive bladder (n = 28), urinary retention (n = 3)
Jones et al[56]	1 woman	32 years	Unspecified	Dysuria (n = 1)
Kelly et al[50]	60 women	57.8 years	Unspecified	Fecal incontinence (n = 60)
Musco et al[52]	41 women; 21 with sexual dysfunction	51 years	Unspecified	Overactive bladder (n = 41)
Zaer et al[34]	287 patients; 130 women and 154 men	49 years	Unspecified	Spinal cord injury (n = 287)
Andy et al[58]	364 women†	63 years	Unspecified	Urgency urine incontinence (n = 364)
Darrow et al[44]	2 women	50 years	Unspecified	Spinal cord injury (n = 2)
de Oliveira et al[48]	24 patients; 15 women, 9 men	41 years	Unspecified	Nonobstructive urinary retention (n = 12); overactive bladder (n = 4); detrusor overactivity with impaired contractility (n = 6); detrusor-sphincter-dyssynergia (n = 1); fecal incontinence (n = 1); multiple sclerosis (n = 1)
Zoorob et al[49]	1 woman	57 years	Unspecified	Overactive bladder (n = 1)
Banakhar and Youness[46]	13 patients; 8 women, 5 men	47 years	Unspecified	Nonobstructive urine retention (n = 5); overactive bladder (n = 3); pelvic pain syndrome (n = 3); impotence (n = 1)
Ismail and Abdullhussein[57]	21 patients; 9 women, 12 men	16–61 years (no average reported)	Unspecified	Urine and/or fecal incontinence (n = 21)
Marinello et al[53]	46 patients; 19 women, 27 men*	62.2 years	Unspecified	Lower anterior resection syndrome (n = 46)

†174 women undergoing sacral nerve stimulation, rest of patients were in onabotulinumtoxinA group.
*16 men and seven women who underwent tibial nerve PNS, rest of patients were in sham group.

Table 3. Cohort Study and Case-Control Study Quality Rating.

Author	Year	Selection	Comparability	Outcome
Neuromodulation studies				
van der Aa et al[40]	1995	*	–	**
van der Aa et al[41]	1999	*	–	*
Jarrett et al[32]	2005	**	–	**
Meloy et al[38]	2006	***	–	*
van Balken et al[54]	2006	***	–	*
Pauls et al[36]	2007	***	–	*
Lombardi et al[43]	2008	***	–	**
Lombardi et al[30]	2008	***	–	**
Zabihi et al[35]	2008	***	–	***
Ingber et al[39]	2009	***	–	***
Gill et al[37]	2011	***	–	**
Signorello et al[55]	2011	***	–	***
Jadav et al[31]	2013	***	–	*
Yih et al[29]	2013	***	–	**
Banakhar et al[47]	2014	***	–	**
Parnell et al[33]	2015	***	–	**
Kelly et al[50]	2016	***	–	*
Musco et al[52]	2016	**	–	**
Zaer et al[34]	2018	***	–	***
de Oliveira et al[48]	2019	***	–	**
Banakhar et al[46]	2021	***	–	*
Ismail et al[57]	2021	***	–	**

Quality of cohort and case-control studies was determined using the Newcastle-Ottawa scale, which evaluates three categories: selection (maximum four stars), comparability (maximum two stars), and outcome (maximum three stars).

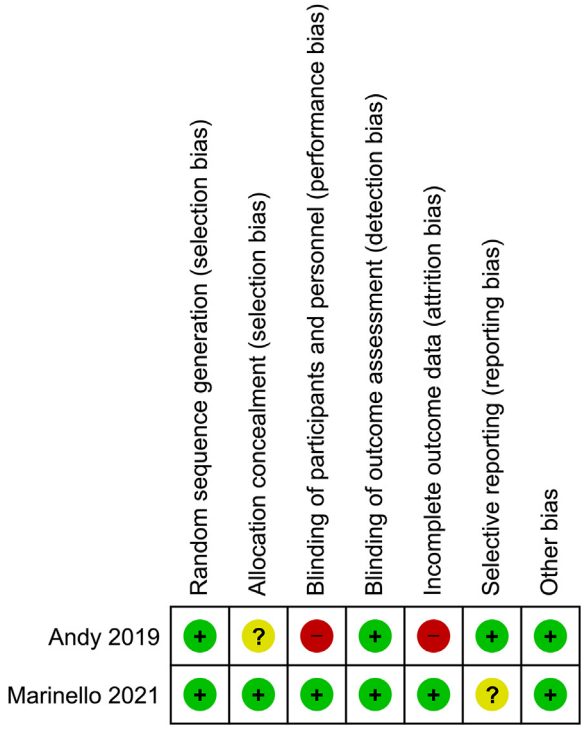

Figure 2. Authors' judgements about each risk of bias item for each included RCT study using the Cochrane risk of bias assessment tool. [Color figure can be viewed at www.neuromodulationjournal.org]

the FSFI as a measurement of female sexual function, nine studies found significant improvements in pain symptoms through the use of sacral nerve stimulation ($n = 305$)[29,30,33,35–37,39,49] or tibial nerve PNS ($n = 21$).[52] The visual analogue scale was used to measure pain in a case report, and it was found that pain decreased after implantation of the sacral nerve stimulator.[42] In another case report that used dorsal column SCS, it also was found that pain decreased after implantation.[45] In a case series that used tibial nerve PNS, it was found that both patients experienced relief in pain symptoms.[51] Two studies assessed changes in dyspareunia using the ePAQ-PF and found improvements through the use of either sacral nerve stimulation ($n = 30$)[31] or tibial nerve PNS ($n = 60$).[50] Results pertaining to FSD are summarized in Table 5.

Statistical Analysis Results

We summarize the effect measures consisting of mean difference and 95% confidence interval for each included study individually in Table 6. Numerical outcome measurements that were reported included FSFI (scaled from 2–36), FSDS (0–52), IIEF-5 (5–25), PISQ-12 (0–48), and ePAQ-PF (0–100). For FSFI, IIEF-5, and PISQ-12, an increase in score indicated an improvement of sexual dysfunction, whereas a decrease in FSDS and ePAQ-PF scores indicated sexual dysfunction improvement. Only ten[29,31,33,39,46,47,50,52,53,55] of the 18 studies that reported numerical outcomes also reported standard deviation values. Among the remaining eight studies, one study[49] was a case report, whereas another study[58] reported a mean difference and p value. The mean difference and 95% confidence intervals could not be calculated in the other six studies.[30,35–37,43,48]

DISCUSSION

In this review, most included studies reported positive improvements in sexual function after neuromodulation interventions. Domains of positive outcomes included erectile function, desire, and satisfaction for men in addition to desire, arousal, orgasm, lubrication, quality of "sex life," intercourse capability and dyspareunia in women. A plausible reason for this positive change is due to the treatment of pain and urinary/bowel disorders through neuromodulation. Treatment and recovery of neurological function, which have been documented with SCS therapy for painful diabetic neuropathy and spinal cord injury, also may play a role in improvement of sexual function.[59–62]

Neuromodulation is a proven therapy for the treatment of pain. In our review of neuromodulation interventions, 18 studies reported outcomes of pain intensity after either sacral nerve stimulation or tibial nerve PNS. Only three studies[46–48] reported no significant changes for pain, whereas the rest reported significant improvement of pain. However, among the three studies that reported no significant change in pain, all three still reported nonsignificant FSFI pain domain improvements. Banakhar and Youness (2021)[46] reported an increase from 3.9 (± 2.1) to 5.6 (± 0.4), with a p value of 0.053. Likewise, Banakhar et al (2014)[47] reported an increase from 2.89 (± 2.66) to 3.5 (± 2.71) (p value = 0.134). Lastly, de Oliveria et al[48] reported an increase from 4.4 to 5.2 (p value = 0.67). A potential reason for these three studies not showing significant improvements in pain may be due to the small sample sizes. Banakhar and Youness (2021), Banakhar et al (2014), and de Oliveria et al analyzed eight, 28, and 15 patients, respectively.[46–48] There have been several proposed mechanisms

Table 4. Results of Male Outcomes.

Study	Primary outcome (sexual dysfunction)	Secondary outcomes	Additional comments
van der Aa et al[40]	Erectile function → improved	Urinary Symptoms → improved Bowel Symptoms → improved	All 14 male patients were able to achieve a full erection with continuous stimulation.
van der Aa et al[41]	Erectile function → improved	Urinary Symptoms → improved Bowel Symptoms → improved	29 of 33 men could maintain a full erection.
van Balken et al[54]	Desire → improved Satisfaction → improved	None	Sexual function was found more likely to improve in female patients and patients with overactive bladder.
Lombardi et al[43]	Erectile function → improved	Urinary Symptoms → improved	None
Zaer et al[34]	Erectile function → declined Ejaculation, orgasm, and intercourse capability → declined	Urinary Symptoms → improved	None
de Oliveira et al[48]	Erectile function → improved	None	None
Banakhar and Youness[46]	Erectile function → improved	None	Change in sexual function was not significantly correlated with age, function diagnosis, or post residual volume.
Ismail and Abdullhussein[57]	Erectile function → improved	Urinary Symptoms → improved Bowel Symptoms → improved	7 of the 9 men who had ED pre-implant no longer experienced ED post-implant.
Marinello et al[53]	Erectile function → declined	Bowel Symptoms → improved	Mean change from baseline sexual function was similar for tibial nerve PNS and control group.

for the improvement of pain from neuromodulation. A common mechanism proposed is the gate control theory.[63] With the emergence of high-frequency waveform, burst waveform, and other new waveform paradigms, new mechanisms have been proposed. For high-frequency SCS interventions, it has been proposed that the gate control mechanism is activated without activating pathways for paresthesia.[64] Another waveform is burst stimulation, which provides variations in firing patterns of the dorsal column of both the lateral and medical aspects of the spinothalamic tract.[65] Similarly, studies on PNS highlight that modulation of higher central nervous system centers may occur, including the dorsal lateral prefrontal cortex, anterior cingulate cortex, and parahippocampal areas.[66,67] Changes in endogenous neurotransmitters and N-methyl-D-aspartate pathways also may be involved.[66]

Neuromodulation also is regularly used for the management of urinary and bowel disorders. In our review, 21 studies reported changes in urinary and/or bowel symptoms, with only one study[58] reporting no change in bowel symptoms, and two studies[42,56] reporting no change in urinary symptoms. Although the mechanisms of neuromodulation for the improvement of urinary and bowel symptoms are still not known, there has been a proposed mechanism by a previous review. Khunda et al[68] proposes that the improvement of urinary and bowel disorders through neuromodulation may be due to stimulation of afferent pathways from the genital area.

Although neuromodulation is not a proven intervention for the treatment of sexual dysfunction, there are potential explanations supporting its efficacy. One possible explanation is that improvements in sexual function come directly from improvements of pain or of urinary or bowel symptoms. Because many domains of sexual function are interconnected, the improvement of one domain often results in the improvement of another. An example would be the improvement of dyspareunia when pelvic pain is treated. Subsequently, the patient may experience a greater desire to engage in sexual activities because they no longer experience as much pain as they did before treatment. The patient also will experience a greater capability to have intercourse and have a better quality of "sex life" because intercourse will not be extremely painful. Another example would be the treatment of urinary symptoms. Urinary symptoms such as incontinence have a negative impact on sexual function because they cause patients to avoid intercourse or may make intercourse less desirable.[69] With improved urinary symptoms, people may experience greater sexual function overall because they will no longer fear being incontinent during intercourse. This was reflected in three of the included studies[31,36,37] that specifically reported that participants experienced improved sexual function directly owing to improved urinary symptoms after sacral nerve stimulation. Zabihi et al[35] and van Balken et al[54] also reported that patients with urinary symptoms demonstrated improvements in sexual function. This claim is further supported by previous reviews that report even stress urinary incontinence that was corrected with surgery resulted in the improvement of sexual function.[68,70] However evidence remains conflicting because three of the included studies[46,47,52] reported no correlation between changes in urinary/bowel symptoms and changes in sexual function.

When discussing the treatment of sexual dysfunction, it is important to note possible mechanistic differences in improvement for neurological vs nonneurological sexual dysfunction from neuromodulation. A major difference is that neurological sexual dysfunction may be improved through the resolution of pain or of urinary or bowel symptoms. Lombardi et al reported larger improvements in the FSDS, an assessment for sexual distress, than in FSFI, an assessment for sexual function.[30] This larger improvement was attributed to the FSDS measurement accounting for the impact of voiding dysfunction on sexual function (ie, the FSDS score improved more because it is related to voiding dysfunction).[30] Other than this difference, neuromodulation mechanisms may be similar for both neurological and nonneurological sexual dysfunction. Sympathetic and parasympathetic nerves both play a role in sexual function. Stimulation of sympathetic nerves results in pelvic contractions for orgasm in women and semen ejection to the posterior urethra in men.[46] Stimulation of parasympathetic nerves results in increased blood flow and vasodilation, both trademarks for current sexual dysfunction interventions.[46] Because neuromodulation works to alter nerve pathways, the mechanism in

Table 5. Results of Female Outcomes.

Study	Primary outcome (sexual dysfunction)	Secondary outcomes	Additional comments
Whiteside et al[45]	Pain → improved	None	After 3 years of implantation, patient reported significant pain improvement in vulvar pain, and was able to have pain-free vaginal sex. Patient also reports resumption of vulvar pain within 6 hours of turning off stimulator, and resolution of pain within 2 hours of turning on stimulator.
Jarrett et al[32]	General "Sex Life" in Women → improved	Bowel Symptoms → improved	7 of the 9 patients experienced improvement in sex life with a 40% median improvement. The percent improvement and age had an inverse relationship ($r = -0.834$, $p < 0.005$).
Meloy and Southern[38]	Lubrication → improved Orgasm → improved Satisfaction → improved	None	4 of 5 secondary anorgasmia patients experienced the return of orgasms. The patients lost the ability to orgasm again once the device was removed. The stimulation was successful in 10 of the 11 patients. Frequency of sexual activities increased after implantation.
van Balken et al[54]	Desire → improved Satisfaction → improved	None	Sexual function was found most likely to improve in female patients and patients with overactive bladder.
Pauls et al[36]	Desire → improved Arousal → no change Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved	Urinary symptoms → improved	Frequency of sex increased significantly after implantation ($p = 0.047$). Three of the seven participants reported improved sexual function through decreased urgency and increased desire after implantation.
Lombardi et al[30]	Desire → improved Arousal → improved Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved General "Sex Life" in women → improved	Urinary Symptoms → improved	Overall sexual distress in patients decreased.
Zabihi et al[35]	Desire → no change Arousal → improved Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved	Urinary symptoms → improved	Improvement of sexual function was greatest in patients with voiding dysfunction.
Ingber et al[39]	Desire → no change Arousal → improved Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved	Urinary symptoms → improved	None
Marcelissen et al[42]	Pain → improved	Urinary Symptoms → no change	Patient was very satisfied with treatment. Pain symptoms were significantly improved.
Gill et al[37]	Desire → improved Arousal → improved Lubrication → improved Orgasm → no change Satisfaction → improved Pain → improved	Urinary symptoms → improved	Most patients had fewer occurrences of incontinence with sexual activity and had less fear of incontinence that would make them restricted with sexual activity.

(Continued)

Table 5. *Continued*

Study	Primary outcome (sexual dysfunction)	Secondary outcomes	Additional comments
Signorello et al[55]	Desire → improved Arousal → improved Lubrication → improved Orgasm → no change Satisfaction → improved Pain → no change	Urinary Symptoms → improved	Slightly better overall improvements were seen in neurogenic patients than nonneurogenic.
Jadav et al[31]	Pain → improved General "Sex Life" in Females → improved	Urinary Symptoms → improved Bowel Symptoms → improved	Overall, patients felt less impact from urinary, bowel, or vaginal symptoms on sex life.
Yih et al[29]	Desire → improved Arousal → no change Lubrication → no change Orgasm → improved Satisfaction → improved Pain → improved	Urinary Symptoms → improved	Of 74 patients who were not sexually active previously, ten patients reported that they were sexually active during follow-up at 12 months.
Banakhar et al[47]	Desire → improved Arousal → no change Lubrication → no change Orgasm → improved Satisfaction → no change Pain → no change	Urinary symptoms → improved	Change in sexual function was not significantly correlated with age, body mass index, diagnosis, or urinary symptoms.
Elkattah et al[51]	Pain → improved	Urinary Symptoms → improved Bowel Symptoms → improved	One patient continued without clitoral pain after treatment. The other patient experienced resolution of clitoral pain but had it return one month after completion of 12 tibial nerve PNS sessions; patient is planning to trial sacral nerve stimulation.
Parnell et al[33]	Desire → improved Arousal → improved Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved	Urinary symptoms → improved Bowel Symptoms → improved	None
Jones et al[56]	Arousal → improved[†]	Urinary Symptoms → no change	Patient continues to report significant improvement in persistent genital arousal two years after implantation.
Kelly et al[50]	Pain → improved General "Sex Life" in Women → improved	Urinary Symptoms → improved Bowel Symptoms → improved	None
Musco et al[52]	Desire → improved Arousal → improved Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved	Urinary Symptoms → improved	No significant correlation was found between changes in OAB-q SF scores and FSFI total scores.
Zaer et al[34]	Intercourse Capability → no change Orgasm → no change	Urinary Symptoms → improved	None
Andy et al[58]	Desire → no change Arousal → no change Orgasm → no change Intercourse capability → improved	Urinary Symptoms → improved Bowel Symptoms → no change	No significant difference between treatment group of sacral nerve stimulation and onabotulinumtoxinA.

(Continued)

Table 5. *Continued*

Study	Primary outcome (sexual dysfunction)	Secondary outcomes	Additional comments
Darrow et al[44]	Orgasm → improved	Urinary Symptoms → improved Bowel Symptoms → improved	One patient reported no improvement in sexual function. The other patient reported return of ability to orgasm returned for the first time since injury. While the stimulation was on and immediately after turning it off, orgasm could be achieved during sexual intercourse.
de Oliveira et al[48]	Desire → no change Arousal → no change Lubrication → improved Orgasm → no change Satisfaction → no change Pain → no change	None	None
Zoorob et al[49]	Desire → improved Arousal → improved Lubrication → improved Orgasm → improved Satisfaction → improved Pain → improved	Urinary symptoms → improved	Patient developed persistent genital arousal in the 6 months after implantation; device had to be explanted, which resulted in a decline in FSFI scores (although still higher scores than baseline pre-implant).
Banakhar and Youness[46]	Desire → improved Arousal → improved Lubrication → no change Orgasm → improved Satisfaction → improved Pain → no change	None	Change in sexual function was not significantly correlated with age, function diagnosis, or post residual volume.
Marinello et al[53]	Overall female sexual function → declined	Bowel Symptoms → improved	Mean change from baseline sexual function was similar for tibial nerve PNS and control group.

OAB-q SF, Overactive Bladder short-form questionnaire.
[†]Improvement in the form of decreased arousal (treated for persistent genital arousal).

Table 6. Mean Differences of Numerical Outcome Assessments.

Study	Scale	Domains evaluated	Preintervention mean (SD)	Postintervention mean (SD)	Mean difference (95% CI)
Pauls et al[36]	FSFI* (2–36)	Overall female sexual function^	20.74 (NR) (n = 7)	30.44 (NR) (n = 7)	–
Lombardi et al[43]	IIEF-5 (5–25)	Erectile function	N†: 14.6 (NR) (n = 29)	N: 18 (NR) (n = 29)	–
			I††: 15.5 (NR) (n = 23)	I: 18 (NR) (n = 23)	–
Lombardi et al[30]	FSFI (2–36)	Overall female sexual function	N: 22.7 (NR) (n = 11)	N: 26.02 (NR) (n = 11)	–
	FSDS (0–52)	Quality of "Sex Life" in women	I: 24.2 (NR) (n = 8)	I: 26.5 (NR) (n = 8)	–
			N: 49.9 (NR) (n = 11)	N: 32.2 (NR) (n = 11)	
			I: 46 (NR) (n = 8)	I: 36.1 (NR) (n = 8)	
Zabihi et al[35]	FSFI (2–36)	Overall female sexual function	12.0 (NR) (n = 36)	18.2 (NR) (n = 36)	–
Ingber et al[39]	FSFI (2–36)	Overall female sexual function	18.67 (6.8) (n = 21)	20.97 (6.0) (n = 21)	2.30 (−1.58 to 6.18)
Gill et al[37]	FSFI (2–36)	Overall female sexual function	22.6 (NR) (n = 8)	25.8 (NR) (n = 8)	–
Signorello et al[55]	FSFI (2–36)	Overall female sexual function	18.4 (4.8) (n = 16)	22.7 (4.5) (n = 16)	4.30 (1.08–7.52)
Jadav et al[31]	ePAQ-PF (0–100)	Dyspareunia	12.4 (19.2) (n = 19)	11.1 (19.4) (n = 19)	−1.30 (−13.57 to 10.97)
		Quality of "Sex Life" in women	38.8 (30.4) (n = 19)	32.8 (34.2) (n = 19)	−6.00 (−26.57 to 14.57)
Yih et al[29]	FSFI (2–36)	Overall female sexual function[2]	13.5 (8.5) (n = 167)	15.9 (8.9) (n = 83)	2.40 (0.09–4.71)
Banakhar et al[47]	FSFI (2–36)	Overall female sexual function	15 (9) (n = 23)	18 (10) (n = 23)	3.00 (−2.50 to 8.50)
Parnell et al[33]	FSFI (2–36)	Overall female sexual function	9.98 (11.2) (n = 21)	12.5 (13) (n = 21)	2.52 (−4.82 to 9.86)
	PISQ-12 (0–48)	Overall female sexual function	24.7 (7.7) (n = 13)	30.9 (7.9) (n = 13)	6.20 (0.20–12.20)
Kelly et al[50]	ePAQ-PF (0–100)	Dyspareunia	33.91 (19.53) (n = 60)	31 (16.89) (n = 60)	−2.91 (−9.44 to 3.62)
		Quality of "Sex Life" in women	50.6 (21.36) (n = 60)	47.87 (28.5) (n = 60)	−2.73 (−11.74 to 6.28)
Musco et al[52]	FSFI (2–36)	Overall female sexual function	17.24 (3.6) (n = 21)	23.78 (7.32) (n = 21)	6.54 (3.05–10.03)
Andy et al[58]	PISQ-12 (0–48)	Intercourse capability	32.7 (6.7) (n = 76)	NR	1.3 (p = 0.11)^~
de Oliveira et al[48]	IIEF-5 (5–25)	Erectile function	10 (NR) (n = 9)	17 (NR) (n = 9)	–
	FSFI (2–36)	Overall female sexual function	24.1 (NR) (n = 15)	26.3 (NR) (n = 15)	–
Zoorob et al[49]	FSFI (2–36)	Overall female sexual function	5.3**	25.2	19.9
Banakhar and Youness[46]	FSFI (2–36)	Overall female sexual function	15 (9) (n = 23)	18 (10) (n = 23)	3.00 (−2.50 to 8.50)
Marinello et al[53]	IIEF-5 (5–25)	Erectile function	9.5 (5.9) (n = 16)	8.5 (6.3) (n = 12)	−1.00 (−5.59 to 3.59)
	FSFI (2–36)	Overall female sexual function	23.4 (6.0) (n = 7)	19.5 (9.7) (n = 6)	−3.90 (−12.84 to 5.04)

PISQ-12, Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire Short form.
*For FSFI, IIEF-5, and PISQ-12: lower score = greater sexual dysfunction (for any other scale listed: higher score = greater sexual dysfunction).
^Overall female sexual function encompasses the domains of desire, arousal, lubrication, orgasm, satisfaction, pain.
†Patients with neurogenic dysfunction.
††Patients with idiopathic dysfunction.
~Reported by the study.
**Case report (no standard deviation).

which it alters nerve pathways for sexual dysfunction may remain unchanged for neurologic and nonneurologic sexual dysfunction.[71]

Despite the overall positive outcomes across studies, this review also identified that some patients experienced negative changes with loss of sexual function. Although this does raise concerns, this finding was only reported in two studies.[34,53] In the study by Zaer et al,[34] participants were asked to reflect on the differences in sexual function for periods as long as 30 years ago. This is problematic because of two main reasons: aging and reporting bias. In the span of up to 30 years, the participant may have developed another sexual disorder or experienced exacerbation of their preexisting sexual dysfunction. It is well researched that as people age, they are at higher risk for experiencing sexual dysfunction.[72] In addition, asking participants to reflect on their symptoms that occurred a long time ago makes egocentric and reporting bias probable. Marinello et al[53] also reported patients experiencing negative changes in sexual function. A possible explanation for the worsening of sexual dysfunction is age. Participants in this study had one of the oldest mean ages compared with other included studies in this entire review (62.2 years). As mentioned in previous reviews, older female populations are more likely to be postmenopausal, resulting in higher incidence of FSD.[73] For male patients, as age increases, so does the incidence of ED.[74] Both may contribute as negative factors that worsen sexual function at a greater magnitude than potential benefits obtained from neuromodulation, thus resulting in worse sexual function outcomes.

An important detail to note is that an overwhelming majority of the studies included in this review used PNS (sacral nerve stimulation and tibial nerve stimulation) rather than dorsal column SCS. The two neuromodulation intervention types are similar in that they both can inhibit pain signals through the gate control theory and other similar mechanisms.[63,64] However, the typical reasons for application of the two stimulation types differ. SCS is used mainly for the purpose of pain management. Common applications are for pain secondary to failed back surgery syndrome, refractory angina pectoris, peripheral arterial disease, complex regional pain syndrome, painful diabetic neuropathy, and nonsurgical low back pain.[75] PNS, in contrast, is not only used for treatment of pain but also may be used for treatment of fecal incontinence, urinary incontinence, voiding dysfunction, and irritable bowel syndrome.[66,76]

The optimization of other medical conditions also may be necessary to address sexual dysfunction. For instance, the biopsychosocial model may play a significant role in the manifestation of sexual dysfunction. Several studies have reported that biopsychosocial factors, including stress, depression, and anxiety, are correlated with lower sexual function.[77,78] Treatments to address the biopsychosocial etiology involve a combination of pharmacotherapy and psychotherapy, with pharmacotherapy alone being inferior to a multimodal strategy.[78,79] In addition, other medical conditions also may need to be optimized and addressed. For example, studies highlight that treatment and optimization of diabetes may be associated with improved sexual dysfunction.[80,81] This applies to many other medical conditions, including endometriosis, which has an increased prevalence of sexual dysfunction.[82]

Limitations in Systematic Review Methodology

Owing to the heterogeneity of outcome measurements and the limited number of studies using the same outcome measure scales, the authors were unable to pool any results for a meta-analysis. In addition, no meta-analysis could be conducted for secondary outcomes because most of the studies reported urinary and bowel symptoms through unspecified methods. Another limitation was that all the studies, except for one,[38] included patients with neurological impairments. This made it infeasible to synthesize a subgroup analysis comparing patients with and without neurological defects. Without this subgroup analysis, it becomes impossible to determine if the improvements in sexual function can be attributed to changes in neurological function, and whether improvement in sexual function can be attained in those without neurological deficits. Lastly, most of the included studies demonstrated medium to high risk of outcome bias, mostly owing to inadequate follow-up time or follow-up rate.

Limitations in Reviewed Studies

As aforementioned, outcome assessments for both primary and secondary outcomes were substantially heterogenous. A meta-analysis on FSFI would have been possible because eight studies[29,33,39,46,47,52,53,55] reported the effect sizes along with mean/standard deviation. However, the population of patients within and across the studies was different, with patients who were diagnosed with a variety of conditions including interstitial cystitis or painful bladder syndrome,[29,39] overactive bladder,[29,33,39,46,47,52] and lower anterior resection syndrome.[53] There also was heterogeneity in intervention types and stimulation protocols. Although this is a review on the effects of all neuromodulation interventions, most studies used sacral nerve stimulation, whereas only five studies[50–54] used tibial nerve PNS, and three studies[38,44,45] used dorsal column SCS. Location and specific nerve targeted varied with each study, and many details regarding stimulation settings, such as frequency and waveform, were not provided. The literature is limited on the efficacy of tibial nerve PNS for sexual dysfunction, which is evident in a previous review article in which only four studies could be included.[73] There also was an uneven distribution of sample sizes across the included studies. Sample sizes ranged from seven[36] all the way to 174.[58] This is problematic because larger studies carry more significant weight on the results obtained. A final limitation relates to the study design. Only two studies[53,58] included a comparative control arm. With these limitations of significant heterogeneity within and across the included studies, it is imperative that the findings of this review be interpreted with caution. The clinical implications of this review, whether in support of or against the efficacy of neuromodulation for improving sexual function, cannot be concretely concluded.

Future Directions

Additional research is warranted in neuromodulation for sexual dysfunction. A major area that needs additional research is the effectiveness in patients with no urinary symptoms or spinal cord injury. Currently, it remains unknown if the improvements in sexual function are due to the treatment of other painful symptoms or to direct improvement of neurological deficits from neuromodulation. In addition, further research is needed to determine the extent to which sexual function improves. It would be interesting to determine whether outcomes of sexual dysfunction from neuromodulation differ based on stimulation parameters that include waveform, amplitude, frequency, and location.[83,84] Research on neuromodulation for sexual dysfunction would benefit from researchers being more transparent about their stimulation protocols. Adverse-event data also need to be highlighted as more evidence accumulates for neuromodulation interventions in this patient population with sexual dysfunction.[85] As the application of

neuromodulation therapy becomes more prominent and common for a variety of disorders, dissemination of accurate information and education for physicians and patients will be paramount.[86] A final important area for further research is on patients with certain risk factors. It is not known whether patients with risk factors such as high preoperative opioid requirements[87,88] or history of genitourinary surgery experience inadequate results.

CONCLUSIONS

Our review synthesized the current literature on neuromodulation interventions for treatment of sexual dysfunction. Our study suggests that there may be promise and potential utility of neuromodulation in improving sexual function. However, the certainty in study findings is limited because of the considerable clinical and methodologic heterogeneity present among included studies. Further powered, comparative, and randomized trials are still warranted to establish definitive evidence.

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Authorship Statements

Max Y. Jin selected the relevant studies, extracted the relevant data, completed bias assessment, and drafted the manuscript (Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusion), with Ryan S. D'Souza and Alaa A. Abd-Elsayed making critical revisions for intellectual content. Ryan S. D'Souza selected the relevant studies, extracted relevant data, and completed bias assessment. Alaa A. Abd-Elsayed developed the conception of research and resolved any discrepancies in the selected studies, extracted data, and bias assessment. All authors approved the final manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.07.004.

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COMMENT

A well conducted and written systematic review in a relatively under-researched area and therefore representing a valuable addition to the literature. An interesting and evolving field with promise for the future for those suffering with sexual dysfunction.

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