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Title: Transcutaneous electrical nerve stimulation to improve female sexual dysfunction symptoms: a pilot study

Running Title: Neuromodulation for female sexual dysfunction

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Dr. Mitchell Berger, Dr. Tim Bruns, Dr. Nick Langhals, and Florence O'Gara designed the study. Dr. Mitchell Berger, Dr. Tim Bruns, and Dr. Nick Langhals obtained funding for the study. Dr. Mitchell Berger and Dr. Priyanka Gupta performed stimulation sessions. Dr. Tim Bruns and Lauren Zimmerman analyzed the data. Dr. Mitchell Berger, Dr. Tim Bruns, and Lauren Zimmerman drafted the manuscript. All authors reviewed and approved the final manuscript.

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Abstract

Objectives: To perform a pilot study using transcutaneous electrical nerve stimulation (TENS) on the dorsal genital nerve and the posterior tibial nerve for improving symptoms of female sexual dysfunction in women without bladder problems. We hypothesize that this therapy will be effective at improving genital arousal deficits.

Materials and Methods: Nine women with general female sexual dysfunction (FSD) completed the study. Subjects received 12 sessions of transcutaneous dorsal genital nerve stimulation (DGNS) (n = 6) or posterior tibial nerve stimulation (PTNS) (n = 3). Stimulation was delivered for 30 minutes at 20 Hz. Sexual functioning was evaluated with the Female Sexual Functioning Index (FSFI), and surveys were also given on general health, urological functioning, and the Patients' Global Impression of Change (PGIC) after treatment. Surveys were given before treatment (baseline), after 6 and 12 weeks of treatment, and 6 weeks after the completion of stimulation sessions.

Results: The average total FSFI score across all subjects significantly increased from 15.3 ± 4.8 at baseline to 20.3 ± 7.8 after 6 sessions, 21.7 ± 7.5 after 12 sessions, and 21.3 ± 7.1 at study

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completion ($p < 0.05$ for all time points). Increases were observed in both DGNS and PTNS subjects. Significant FSFI increases were seen in the sub-domains of lubrication, arousal, and orgasm, each of which is related to genital arousal. Bladder and general health surveys did not change across the study. PGIC had a significant increase.

Conclusions: This study provides evidence that transcutaneous stimulation of peripheral nerves has the potential to be a valuable therapeutic tool for women with FSD.

Key words: female sexual dysfunction; genital arousal; dorsal genital nerve; posterior tibial nerve; electrical stimulation

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Introduction

Female sexual dysfunction (FSD) affects 40-45% of adult women and is a difficult condition to diagnose and treat[1,2]. Low genital arousal and poor lubrication affects between 8-28% of women and orgasm difficulties affect 16-25% [2,3], and can be due to underactive neural or vascular activity in the genitals, urological problems, or other pelvic floor dysfunctions [4]. Low sexual desire, or interest, affects 9-39% of women [2,5], and may be due to hyperactivity in prefrontal areas of the brain [4]. Women are more likely to have FSD as they age, and women often have more than one form of FSD [2]. An active and satisfying sex life is widely regarded not only as desirable but as a sign of emotional and physical health. The sexually disinterested person with arousal difficulties is made to feel deficient, dissatisfied or dysfunctional[6]. Medical providers and therapists are challenged by treatment as there are multiple possible contributors and different forms of FSD. Hormone therapy can be effective for genital and desire dysfunctions, but is not recommended for all individuals and is typically not recommended for long-term treatment [7]. Flibanserin, a recently FDA-approved drug, has some success in increasing sexual desire but does not impact genital arousal [8,9]. Sildenafil has occasionally been reported to improve genital arousal [10], but results are inconsistent and frequently present with mild to moderate side effects such as headaches, flushing, rhinitis, and nausea[11]. There is a need for an effective treatment for women who have genital arousal deficiencies without concurrent side effects.

Peripheral neuromodulation therapies have been implemented for patients with bladder dysfunction for decades. Sacral neuromodulation (SNM) involves the surgical implantation of a stimulation system, with an electrode near the S3 sacral foramen delivering continuous stimulation [12].

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Dorsal genital nerve stimulation (DGNS) is typically delivered transcutaneously above the clitoris and lateral to the labia majora in women [13–15], though percutaneous electrodes may also be used [16]. The dorsal genital nerve is a distal branch of the pudendal nerve, which is stimulated centrally with SNM. Percutaneous tibial nerve stimulation (PTNS) is a treatment where patients receive 30 minutes of electrical stimulation a week for 12 weeks with periodic maintenance sessions thereafter [17,18], though benefits have been observed after as few as 6 sessions [19]. Stimulation is delivered via a percutaneous needle placed at the tibial nerve near the ankle, but cutaneous stimulation with transcutaneous electrical nerve stimulation (TENS) electrodes have also shown efficacy in some studies [20–22]. The underlying mechanisms of these neuromodulation therapies are not well understood, with evidence suggesting inhibition at spinal and/or supra-spinal levels affecting efferent control over bladder storage and emptying [19,23].

In clinical studies in which patients received neuromodulation treatment for bladder dysfunction, significant improvements in sexual functioning as evaluated with the Female Sexual Function Index (FSFI) were noted in both SNM [24–27] and PTNS [28–30] therapies. While bladder dysfunction has a known negative effect on sexual function[31,32], improvements in sexual functioning were found to be independent from improvements in bladder functioning [25,30], indicating that the neuromodulation may have a direct impact on genital arousal. No studies have evaluated the effects of peripheral nerve stimulation specifically on patients with FSD, without an underlying urological condition.

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The goal of this pilot study was to evaluate weekly skin-surface TENS of the dorsal genital nerve and the posterior tibial nerve for improving sexual function in women with FSD and no clinically-diagnosed bladder problems.

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Methods

Approval for this study was obtained from the Michigan Medicine Institutional Review Board (IRB) prior to initiation (study number HUM00101713). Participants were recruited through Michigan Medicine sexual health practices, gynecology clinics, and an online University of Michigan health research portal (umhealthresearch.org). This study was registered at clinicaltrials.gov under identifier NCT02692417.

In a phone call with a study coordinator, subjects were screened for study eligibility. All subjects were 18 years or older cis-gender women, neurologically stable, and sexually active at least once a month. The short-form Female Sexual Function Index (FSFI-6) was used to screen for FSD, with scores below 19 required for inclusion [33]. The specific type or types of FSD that each participant had was not identified as part of the screening process. Women who were pregnant or planning pregnancy, had clinically diagnosed bladder dysfunction or pelvic pain, previous pelvic surgery, experience with electrical stimulation for bladder or sexual problems, recent use of TENS on their pelvis, back or legs, had an implanted pacemaker, defibrillator, spinal cord stimulator, or other nerve stimulator, or were taking any investigational drug were excluded from the study. All subjects provided written informed consent. A pregnancy test was also performed at the first session to confirm nongravidity if the subjects were premenopausal and had not had a hysterectomy.

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Menopause status was not specifically tracked across participants. The intended sample size of this study was 20 subjects, with 10 subjects in each study group, similar to other neuromodulation pilot studies [13,14,34]. As described below, a smaller sample size was reached due to challenges in subject recruitment and retention.

At the first stimulation session, patients were randomized into one of two study groups, DGNS or PTNS. Randomization was accomplished using a random-number table and block size of two. Allocation assignment was performed using sequentially numbered, opaque sealed envelopes, which were opened in the presence of the subjects. Subjects received skin-surface stimulation with a transcutaneous electrical nerve stimulation (TENS) unit (Empi Select, DJO Global, Vista, CA). Electrodes were 1.25-inch round neurostimulation electrodes (ValuTrode Fabric CF3200, Axelgaard Manufacturing Co., Ltd., Fallbrook, CA). For DGNS participants, each electrode was placed on either lateral side of the clitoris [15]. For PTNS participants, electrodes were placed just above the medial malleolus and the ipsilateral calcaneus [21,22]. Stimulation for both arms was applied at 20 Hz, as is typical for PTNS [35]. For both DGNS and PTNS subjects, starting from a low amplitude, current was increased until the participant expressed discomfort, and then reduced to a comfortable level, or a maximal level of 60 mA was reached. Subsequently, stimulation was applied using that amplitude for 30 minutes, at 20 Hz.

Participants completed a total of twelve stimulation sessions [12,17,35]. Our goal was to schedule sessions on consecutive weeks for the duration of participation. However, scheduling conflicts, holidays, and other events led to variations in intra-session intervals across subjects. Participants were compensated for their time.

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Patients completed a series of validated clinical surveys as outcome measures at baseline, after six stimulation sessions, after twelve stimulation sessions, and six weeks after the final session. At all survey intervals, participants completed the full Female Sexual Function Index (FSFI) [36], the short-form 36-question (SF-36) quality of life survey [37], and the 6-question American Urological Association Symptom Index (AUASI) bladder symptom index [38]. At the 6-week and later survey intervals participants also completed the one-question Patients' Global Impression of Change (PGIC) [39]. All surveys were completed and stored through a secure online portal (REDcap)[40].

Comparisons between FSFI, SF-36, AUASI, and PGIC scores at different time points were analyzed with related-samples Wilcoxon signed rank tests with a significance level of 0.05. Tests were run with DGNS and PTNS arms separately as well as pooled together. Where appropriate, values are presented as mean ± standard deviation.

Results

Sixteen subjects were enrolled in the study (Figure 1). Seven subjects dropped out of the study during intervention, due to scheduling conflicts (n = 6) and an adverse event (n = 1; described below). Of the 9 subjects that completed the study, the average age was 46.2 ± 14.5, with a minimum age of 23 and maximum of 66 (Table 1). One subject who was enrolled, but did not receive stimulation, did not complete the demographics survey.

Stimulation was not always delivered in exact 1-week intervals. The average days between sessions was 12.5 ± 10.3 days. The stimulation current amplitude that was delivered ranged from 2.5

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mA to 60.0 mA. Stimulation was delivered at 24.3 ± 18.6 mA for DGNS subjects, and 60.0 ± 0.0 mA for PTNS subjects.

All women began the study with an FSFI total score below the clinical cut-off for diagnosing FSD (26.55) [41], with an average initial score of 15.3 ± 4.8. Overall sexual function significantly increased at 6 weeks, 12 weeks, and 18 weeks from baseline (Figure 2, Table 2). Three of the 9 subjects (33.3%) reached an FSFI score above the clinical cut-off for FSD, and another participant scored just below the threshold (26.4). Four subjects (1 DGNS, 3 PTNS) had a clinically relevant increase in their FSFI score, with an improvement of at least 50%. Arousal and orgasm FSFI sub-scores had significant improvements at 6 weeks, 12 weeks, and 18 weeks from baseline (Figure 3, Table 2) Lubrication FSFI sub-scores had a significant improvement at 12 weeks over baseline (Figure 3, Table 2). Each of the other FSFI sub-scores (desire, satisfaction, pain) had non-significant increases in their scores (Figure 3, Table 2).

Changes in FSFI scores were not related to variations in the intervals between stimulation sessions. The FSFI percent increase had no relationship with average stimulation session intervals at 12 weeks ($y = -0.077x + 40.58$, $R^2 = 0.0139$, $p = 0.78$) or at 18 weeks ($y = -0.1309x + 57.97$, $R^2 = 0.026$, $p = 0.70$).

Overall, participants perceived an improvement in sexual function, as PGIC scores were 3.3 ± 2.0 at 6 weeks (3.0 = "a little better"), 4.0 ± 1.9 at 12 weeks (4.0 = "somewhat better"), and 4.1 ± 1.9 at 18 weeks. These scores are each significantly different from a PGIC score of 1.0 ($p = 0.018$, $p = 0.011$, $p = 0.011$, respectively), which would indicate "no change or worse". The three women (2 PTNS, 1 DGNS) who achieved FSFI scores above the FSD clinical cutoff scored either a 5

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("moderately better") or 6 ("better") at each time point. Overall quality of health scores from the SF-36 remained generally stable across the study duration. The SF-36 category of role limitations due to physical health improved from 88.9% pre-treatment to 97.2% at the 18-week time point across all subjects. Also the SF-36 category emotional well-being showed a significant worsening from 80.0% pre-treatment to 74.2% at week 6 ($p = 0.042$) for DGNS subjects. Participant's bladder functioning, as scored by the AUASI, did not show significant change across all subjects across the study time points, except for the domain of nocturia. There was a significant 25.0% reduction in nocturia symptoms ($p = 0.046$) from baseline (1.78 ± 1.30) to the 18-week time-point (1.33 ± 1.22).

Subjects were given the opportunity to refrain from answering questions. The unanswered questions were scored as a 0, which negatively affected FSFI scoring. Three DGNS subjects (blue/white square, blue/grey square, blue/black square in Figs. 2 & 3) refrained from answering questions about pain. Two of those subjects (blue/grey square, blue/black square) also refrained from answering some of the questions about satisfaction in two surveys. One of those subjects (blue/black square) also refrained from answering some of the questions about lubrication in one survey. One subject (red/black star) reported that between week 12 and week 18 surveys, she was diagnosed with a severe pelvic infection from E. coli. She indicated that this unrelated event would negatively impact her 18-week survey, as seen by declines in her scores from week 12 to week 18, particularly in pain (Fig. 3).

One participant receiving PTNS withdrew from the study after 3 sessions after feeling sciatic nerve pain during stimulation. The subject had a history of sciatic pain. Aggravation reemerged after

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both lowering the amplitude of current delivered and switching the stimulation location to the alternate leg.

Discussion

In this study we demonstrate the feasibility of transcutaneous stimulation as a treatment for genital arousal disorders in women. Significant improvements were achieved in the areas of arousal, lubrication, and orgasm (Fig. 3, Table 2), leading to overall better sexual functioning (Fig. 2). These domains are each related to genital arousal. Subjects reported the highest sexual functioning at 12 weeks into the study, after having received all stimulation sessions. A slight decrease in overall FSFI scores occurred at 18 weeks, after a 6-week washout period without stimulation, suggesting that maintenance sessions may be beneficial. Maintenance sessions are common for patients receiving PTNS for bladder symptoms, with patients receiving a stimulation session every 2-4 weeks after the initial 12 weeks of therapy to maintain the therapeutic benefits [42]. The subjects in the PTNS arm had a greater improvement in sexual functioning (Table 2), but the imbalance of subjects in each arm makes it difficult to perform any statistical comparisons. As 100% of PTNS subjects increased their total FSFI score by at least 50%, compared to 16.7% of the DGNS group, it is possible that PTNS is a more effective treatment modality, although further studies with larger sample sizes are needed. Two PTNS subjects commented that they planned to purchase their own TENS equipment to continue treatment at home after study completion.

Across all subjects the average total FSFI score increased by 6.4 (Table 2). This increase is comparable to or greater than recent clinical trials studying other treatments for women with desire

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and/or arousal subtypes of FSD. In the BEGONIA trial investigating FDA-approved flibanserin for hypoactive sexual desire, the treatment group total FSFI score improved by 5.3 against the placebo group increase of 3.5 [8], while a study of bremelanotide saw a total FSFI increase of 4.4 in the most effective treatment group against a placebo increase of 1.9.[43] Clinical studies of neuromodulation, which presumably would benefit genital arousal disorders over hypoactive sexual desire, have reported a total FSFI score increase of 6.5 in a group of patients receiving PTNS for OAB [30] and 4.3 in a group of patients with sacral neuromodulation implants [44], with other SNM and PTNS neuromodulation studies reporting even smaller FSFI increases (range: 2.1-3.3) [24–27,29]. That our FSFI increase was comparable to or higher than neuromodulation studies using invasive stimulation electrodes suggests that non-invasive transcutaneous stimulation can yield effective results. A larger, controlled study is needed to verify that we did not have an overall placebo effect higher than those reported in the flibanserin and bremelanotide studies. The non-significant increases in non-genital arousal related FSFI sub-domains (desire, satisfaction, pain; Fig. 3, Table 2) could indicate that stimulation led to benefits in these areas, either directly or indirectly through improvements in genital arousal, or those increases may relate to any general placebo effects that occurred in our study.

These results provide further evidence that the improvements to sexual functioning seen in neuromodulation studies for bladder dysfunction are a direct result of the therapy, as opposed to a secondary result from treated bladder symptoms. Peripheral nerve stimulation could be used as a clinical tool to treat women with genital arousal deficiencies. Women who may benefit from this treatment have a variety of potential underlying conditions, including diabetes-related complications, neurological conditions such as multiple sclerosis and spinal cord injury, and side effects of hormonal

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changes, trauma, and even childbirth [4,5,45,46] . A potential mechanism in the observed improvements in genital arousal in our study is an increase in pelvic blood flow, as has been modeled by preclinical studies investigating similar stimulation techniques [47,48], however more research is needed.

An important limitation in this study is the lack of a control. As the results are based on patient-reported outcomes, the impact of a placebo effect could be considerable. Neither the researchers nor the subjects were blinded. There were challenges in recruitment for the study, but more notably in retention. Two primary factors were a need for weekly stimulation sessions during normal business hours and the location of the clinical research center, which required a car or bus to reach. Six of the 7 subjects who discontinued the study were in the PTNS arm (Fig. 1), leading to an unequal distribution of subjects. Once enrolled, it was also difficult to schedule subjects every week, so most did not complete the study in the expected 18 weeks. This was due to both patient scheduling conflicts as well as clinician availability. Although the stimulation session intervals often differed from standard PTNS clinical practice for bladder symptoms, no effect on our results was observed. Finally, skin-surface transcutaneous stimulation was utilized, and though it has been shown to be effective clinically [15,49,50], it is less specific than percutaneous needles.

Future studies with sham or placebo controls, as have been completed for bladder care, are necessary to confirm the efficacy of this treatment modality[17]. In addition, percutaneous stimulation could be used for more accurate recruitment of target nerves.

Conclusion

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This study provides further evidence that improvements seen in the sexual functioning of women receiving neuromodulation treatment for bladder dysfunction were independent of improvements in bladder symptoms, and that stimulation can have a direct impact on sexual arousal. Improvements were primarily seen in genital arousal components of sexual functioning, including lubrication, arousal, and orgasm. Thus this pilot study demonstrates the feasibility of using transcutaneous neuromodulation of peripheral nerves to treat symptoms of female sexual dysfunction.

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Authorship Statements

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Dr. Mitchell Berger, Dr. Tim Bruns, Dr. Nick Langhals, and Florence O'Gara designed the study. Dr. Mitchell Berger, Dr. Tim Bruns, and Dr. Nick Langhals obtained funding for the study. Dr. Mitchell Berger and Dr. Priyanka Gupta performed stimulation sessions. Dr. Tim Bruns and Lauren Zimmerman analyzed the data. Dr. Mitchell Berger, Dr. Tim Bruns, and Lauren Zimmerman drafted the manuscript. All authors reviewed and approved the final manuscript.

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Table 1. Patient demographics.

Category	All enrolled participants	PTNS completed	DGNS completed
Total	16	3	6
Age (years)	40.9 ± 15.0	37.3 ± 19.1	50.7 ± 11.0
BMI (kg/m^2)	26.8 ± 4.4	28.4 ± 5.0	26.3 ± 4.9
Race/Ethnicity			
White	10 (67%)	2 (67%)	6 (100%)
Black	1 (7%)	1 (33%)	0 (0%)
Asian or Pacific Islander	1 (7%)	0 (0%)	0 (0%)
Other	3 (20%)	0 (0%)	0 (0%)
Relationship status			
Single	2 (13%)	0 (0%)	1 (17%)
Non-married relationship	3 (20%)	1 (33%)	0 (0%)
Married	10 (67%)	2 (67%)	5 (83%)
On prescription antidepressant	6 (40%)	2 (67%)	3 (50%)
Baseline FSFI	17.1 ± 5.0	15.2 ± 5.3	15.5 ± 4.6
Baseline SF-36	83.1 ± 11.6	87.9 ± 4.4	80.5 ± 9.0
Baseline AUASI	6.4 ± 5.3	9.3 ± 6.4	4.5 ± 2.9

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Table 2. Average FSFI scores across all subjects as well as across two subject groups, with standard deviation in (). Statistical significance ($p < 0.05$), as compared between each study time point and baseline, indicated in bold with *.

	Desire	Arousal	Lubrication	Orgasm	Satisfaction	Pain	Total
All (n=9)							
Baseline	2.3 (1.0)	2.2 (0.9)	2.8 (1.5)	2.7 (1.7)	2.7 (1.1)	3.3 (1.8)	15.3 (4.8)
6 weeks	2.7 (1.3)	**3.3 (1.3)***	4.1 (1.7)	**3.8 (1.7)***	3.8 (1.8)	4.6 (1.8)	**20.3 (7.8)***
12 weeks	3.0 (1.2)	**3.6 (1.4)***	**3.7 (1.5)***	**3.8 (1.5)***	3.8 (1.7)	4.9 (2.3)	**21.7 (7.5)***
18 weeks	2.7 (1.3)	**4.0 (1.4)***	3.8 (1.5)	**4.4 (1.6)***	4.3 (1.8)	4.1 (2.1)	**21.3 (7.1)***
DGNS (n=6)							
Baseline	2.3 (1.0)	2.3 (1.0)	2.9 (1.6)	2.7 (2.0)	2.6 (1.4)	3.5 (2.3)	15.2 (5.3)
6 weeks	2.0 (1.0)	2.8 (1.0)	3.3 (2.1)	3.8 (1.6)	3.2 (2.1)	4.5 (2.3)	17.4 (6.6)
12 weeks	2.5 (1.2)	3.0 (1.1)	**3.6 (1.4)***	3.5 (1.6)	3.1 (1.7)	4.5 (2.2)	**18.7 (6.9)***
18 weeks	2.2 (0.8)	**3.7 (1.4)***	4.1 (1.2)	4.1 (1.7)	3.5 (1.9)	4.1 (2.6)	**18.8 (5.4)***
PTNS (n=3)							
Baseline	2.4 (1.2)	2.1 (0.9)	2.5 (1.5)	2.5 (1.2)	2.9 (0.2)	3.1 (1.3)	15.5 (4.6)
6 weeks	4.0 (0.7	4.4 (1.5)	4.4 (2.3)	3.9 (2.3)	4.7 (1.0)	4.7 (1.4)	26.0 (7.8)
12 weeks	4.0 (0.3)	4.9 (0.9)	4.1 (2.0)	4.3 (1.3)	5.2 (0.0)	5.3 (0.6)	27.8 (4.8)
18 weeks	3.8 (1.5)	4.6 (1.5)	3.4 (2.3)	4.9 (1.5)	5.3 (1.2)	4.1 (2.2)	26.2 (8.6)

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Figure Legends

Figure 1. Study CONSORT flow diagram.

Figure 2. Average total FSFI score for all subjects (PTNS and DGNS) at each survey time point. Error bars give standard error of the mean. Significant improvement from baseline occurred at each time point. Individual icons are unique for each participant, with PTNS participants indicated with stars and DGNS participants indicated with circles and squares. White, grey, and black shading inside of each icon further distinguishes between different subjects. Within each study week, icon order from left to right indicates study participation order. (*, $p < 0.05$; **, $p < 0.01$)

Figure 3. Individual FSFI sub-domain scores for all subjects. The pooled mean is given by the horizontal bar. Individual icons are unique for each participant, following the convention in Fig. 2. Within each study week, icon order from left to right indicates study participation order. (*, $p < 0.05$)

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