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The Diagnostic Role of Neurophysiological Tests for Premature Ejaculation: A Prospective Multicenter Study

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Study Need and Importance: Premature ejaculation (PE) is one of the most common male sexual dysfunctions. Local anesthetics (LAs) and dapoxetine are frequently used to treat PE; however, previous literature reported variable efficacy. In our previous studies, we found neural electrophysiological differences among PE patients. This study aims to evaluate the efficacy of LAs and dapoxetine using a novel classification based on neurophysiological tests.

What We Found: This multi-center cohort study enrolled adult men (568) with an intravaginal ejaculatory latency time (IELT) ≤ 2 minutes from 2015 to 2017. The men were divided into 4 groups according to the results of neurophysiological tests and assigned different treatments for 12 weeks: 1) penile sensory hyperexcitability type (Sens)—LAs; 2) penile sympathetic hyperexcitability type (Symp)—dapoxetine; 3) mixed type (Mixed)—both LAs and dapoxetine; and 4) normal type (Norm)—both LAs and dapoxetine. Self-estimated IELT and patient-reported outcomes were recorded.

After the 12-week treatment course, the total percentage of men achieving IELT >2 minutes and ≥ 5 minutes were 82.7% and 76.7%, respectively (see figure). For those with abnormal results of neurophysiological tests (Sens, Symp, and Mixed), 401 (86.6%) had improved IELT >2 minutes, in which 375 (81.0%) achieved IELT ≥ 5 minutes. All patient-reported outcome measures improved in each group after treatment, with greater improvements among those with abnormal neurophysiological tests.

Limitations: The main limitations of this study include the nonrandomized, nonplacebo design and the use of self-estimated IELT to avoid affecting the mood of sexual intercourse by using the stopwatch.

Interpretation for Patient Care: The efficacy of LAs and dapoxetine increased in PE patients with abnormal results of neurophysiological tests. This classification of PE using neurophysiological tests could help guide and improve efficacy of PE therapies.

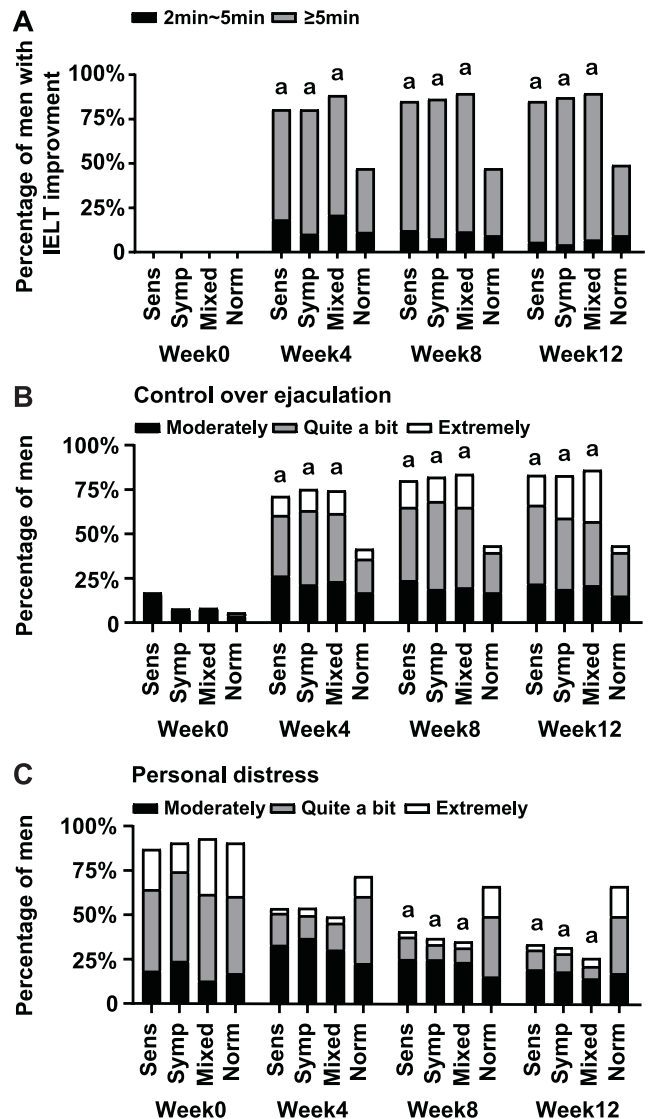


Figure. Percentage of men with improved IELT, control over ejaculation and personal distress over time. a, $p < 0.05$ compared with Norm group.

The Diagnostic Role of Neurophysiological Tests for Premature Ejaculation: A Prospective Multicenter Study

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Purpose: Premature ejaculation (PE) is one of the most common male sexual dysfunctions. Local anesthetics (LAs) and dapoxetine are frequently used to treat PE; however, previous studies show variable efficacy. This study aims to determine the efficacy of LAs and dapoxetine using a novel classification based on neurophysiological tests.

Materials and Methods: This multicenter cohort study enrolled adult men (568) with an intravaginal ejaculatory latency time (IELT) ≤ 2 minutes. Patients were divided into 4 groups according to the results of neurophysiological tests and assigned different treatments for 12 weeks: 1) penile sensory hyperexcitability type (Sens)—LAs; 2) penile sympathetic hyperexcitability type (Symp)—dapoxetine; 3) mixed type (Mixed)—both LAs and dapoxetine; 4) normal type (Norm)—both LAs and dapoxetine. Self-estimated IELT and patient-reported outcomes were recorded.

Results: The total percentage of men achieving IELT > 2 minutes and ≥ 5 minutes after treatment were 82.7% and 76.7%, respectively. For men with abnormal results of neurophysiological tests, 401 (86.6%) had improved IELT > 2 minutes after the 12-week treatment course, in which 375 (81.0%) achieved IELT ≥ 5 minutes. All patient-reported outcome measures improved in each group after 12 weeks of treatment, with greater improvements among those with abnormal neurophysiological tests.

Abbreviations and Acronyms

CGI-C = Clinical Global Impression of Change

CIPE = Chinese Index of Premature Ejaculation

DNSEP = somatosensory evoked potentials of the dorsal nerve

GPSEP = somatosensory evoked potentials of the glans penis

IELT = intravaginal ejaculatory latency time

LA = local anesthetic

Mixed = mixed type

Norm = normal type

PE = premature ejaculation

PEDT = Premature Ejaculation Diagnosing Tool

PEP = Premature Ejaculation Profile

PSSR = penile sympathetic skin response

Sens = penile sensory hyperexcitability type

SEP = somatosensory evoked potential

SSRI = selective 5-serotonin reuptake inhibitor

Symp = penile sympathetic hyperexcitability type

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Conclusions: The efficacy of LAs and dapoxetine increased in PE patients with abnormal results of neurophysiological tests. This novel classification of PE using neurophysiological tests could help guide and improve efficacy of PE therapies.

Key Words: premature ejaculation; anesthetics, local; serotonin uptake inhibitors; neurophysiological monitoring

PREMATURE ejaculation (PE) is one of the most common male sexual dysfunctions, impacting 20%–30% of men.¹ Lifelong PE is defined as ejaculation which always or nearly occurs prior to or within about 1 minute of vaginal penetration from the first sexual experiences.² This occurs on all or nearly all vaginal penetrations and confers negative personal consequences. Local anesthetics (LAs) and selective 5-serotonin reuptake inhibitors (SSRIs) have been shown to be effective in the treatment of PE by increasing intravaginal ejaculatory latency time (IELT) and improving patient satisfaction.² LAs include topical formulations of lidocaine and/or prilocaine and extend IELT by reducing the sensitivity of the penis.³ SSRIs, traditionally used as oral antidepressant medications, are theorized to inhibit neural pathways involved in ejaculation within the central nervous system by increasing synaptic availability of 5-serotonin.⁴ However, the effects of these treatments are variable, with 57%–74% of patients treated with LAs achieving IELT >2 minutes^{5,6} while only 29%–31% of men treated with dapoxetine, the SSRI specifically used to treat PE, were able to achieve IELT >3 minutes.⁷

In our previous studies, we examined the somatosensory and autonomic pathways involved in PE and found neural electrophysiological differences among PE patients.^{8–10} Hyperexcitability of the ejaculatory reflex, which involves hypersensitivity of the glans, accelerated conduction and cortical amplification of genital stimuli, was linked to PE but was only found in 60% of lifelong PE patients.⁸ Additionally, our study found the latency of the sympathetic response to stimulation of penile skin of PE patients was significantly reduced compared to controls, suggesting a hyperexcitable sympathetic response.⁹ Subsequently, sertraline, an SSRI, was shown to reduce the excitability of the sympathetic nervous system in PE patients.¹⁰ Furthermore, the ratio of patients achieving IELT >2 minutes after treatment with sertraline was higher among patients with sympathetic hyperexcitability than patients with normal sympathetic excitability (91.7% vs 17.6%, $p=0.021$).¹⁰ In this prospective multicenter cohort study, we describe a novel classification of PE according to neurophysiological parameters to guide selection of pharmacological treatments for PE.

PATIENTS AND METHODS

Study Design and Participants

The cohort study was designed by investigators in the Department of Andrology of Drum Tower Hospital, Nanjing University. The study was carried out in accordance with the Declaration of Helsinki and reported based on the Consolidated Standards for Reporting Trials statement. The protocol and informed consent form were approved by the Ethics Committees of all participating medical centers (IRB No. 2015-053-01). This study was conducted across 4 medical centers in Jiangsu Province, China from October 2015 to July 2017. It was prospectively registered on ClinicalTrials.gov (NCT02572037).

Inclusion criteria consisted of: 1) men aged between 18 and 60; 2) in stable heterosexual, monogamous relationships over 6 months; 3) ejaculation always or nearly always occurring prior to or within 2 minutes of vaginal penetration^{11,12} from the first occasion of sexual intercourse; 4) the inability to delay ejaculation; and 5) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy. Exclusion criteria consisted of: 1) evidence of urinary tract infection on laboratory testing of urine or prostatic fluid; 2) abnormal sex hormones; 3) comorbid conditions including hypertension, diabetes mellitus, alcohol dependence syndrome, coronary artery disease, and psychiatric disorder; 4) abnormal physical examination findings including abnormal palpation of external genitals, testis, epididymis, and spermatic cord; 5) previous pharmacological therapy for the treatment of PE, including LA, SSRI, phosphodiesterase 5 inhibitor, and tramadol etc; 6) known drug allergy to amide-type LAs or SSRIs; 7) currently participating in or in the past 30 days quit another clinical trial; 8) alcohol or substance abuse in the past 6 months; and 9) erectile dysfunction with diagnosis from a physician or an International Index of Erectile Function-5 total score below 22.

Procedures

Subjects were divided into 4 groups according to results of the neurophysiological tests and given corresponding medications:

1) Penile sensory hyperexcitability type (Sens): with low latency of somatosensory evoked potentials (SEPs) of the glans penis (GPSEP, below 40.83 ms) and/or dorsal nerve (DNSEP, below 39.03 ms).⁸ The Sens group was treated with compound lidocaine cream (2.5% prilocaine and 2.5% lidocaine, Ziguang Pharmaceutical Co. Ltd, Beijing, China; SFDA approval No. H20063466) using 2.5 gm of cream applied topically to the penis for 5 minutes, then washing off prior to sexual intercourse.

2) Penile sympathetic hyperexcitability type (Symp): with low latency of penile sympathetic skin response (PSSR; below 1,184.6 ms).¹⁰ The Symp group was treated with dapoxetine hydrochloride tablet (Berlin-Chemie AG, Berlin, Germany; SFDA approval No. H20150563) using 30 mg or 60 mg, if 30 mg was not effective, orally 1–2 hours before sexual intercourse.

3) Mixed type (Mixed): with both low latency of SEPs (GPSEP and/or DNSEP) and PSSR. The Mixed group was treated with a combination of compound lidocaine cream and dapoxetine with the same dosing as described above, respectively.

4) Normal type (Norm): with normal latency of GPSEP, DNSEP and PSSR. The Norm group was empirically treated with both compound lidocaine cream and dapoxetine with the same dosing as described above, respectively.

All subjects were required to report their results to investigators by clinic appointment or telephone call every 4 weeks for 3 reporting sessions. Subjects were required to report adverse events to investigators immediately or at their scheduled visit, depending on severity. All subjects provided signed, written informed consent, and received travel compensation at each clinic visit.

Neurophysiological Tests

Among the 4 centers involved in this study, 2 centers used the Nicolet® Viking Quest® Electromyograph/Evoked

Potential device (Natus Medical Inc., Middleton, Wisconsin), 1 center used Dantec® Keypoint® electromyograph and evoked potential equipment (Alpine BioMed ApS, Copenhagen, Denmark) and 1 center used Neuropack® electromyograph, nerve conduction velocity and evoked potential measuring system (Nihon Kohden Corp., Tokyo, Japan). The parameters and methods of the SEPs and PSSR recordings were conducted according to our previous publications.^{8,9} To ensure the consistency of data from all centers, the neurophysiological test equipment settings were checked and tested by the same investigator from Drum Tower Hospital on the same healthy volunteers. All investigators and technicians were trained with the same protocol.

Outcome Measures

The primary end point was self-estimated IELT¹³ for each reported intercourse. Patient-reported outcomes were also measured, including the Premature Ejaculation Profile (PEP; at week 0, 4, 8 and 12), Premature Ejaculation Diagnosing Tool (PEDT; at week 0 and 12), Chinese Index of Premature Ejaculation (CIPE; at week 0 and 12) and Clinical Global Impression of Change (CGI-C; at week 0 and 12) (supplementary table, <https://www.jurology.com>).

Statistical Analysis

We hypothesized a 10% increase in reported effectiveness among the matched testing therapeutics groups

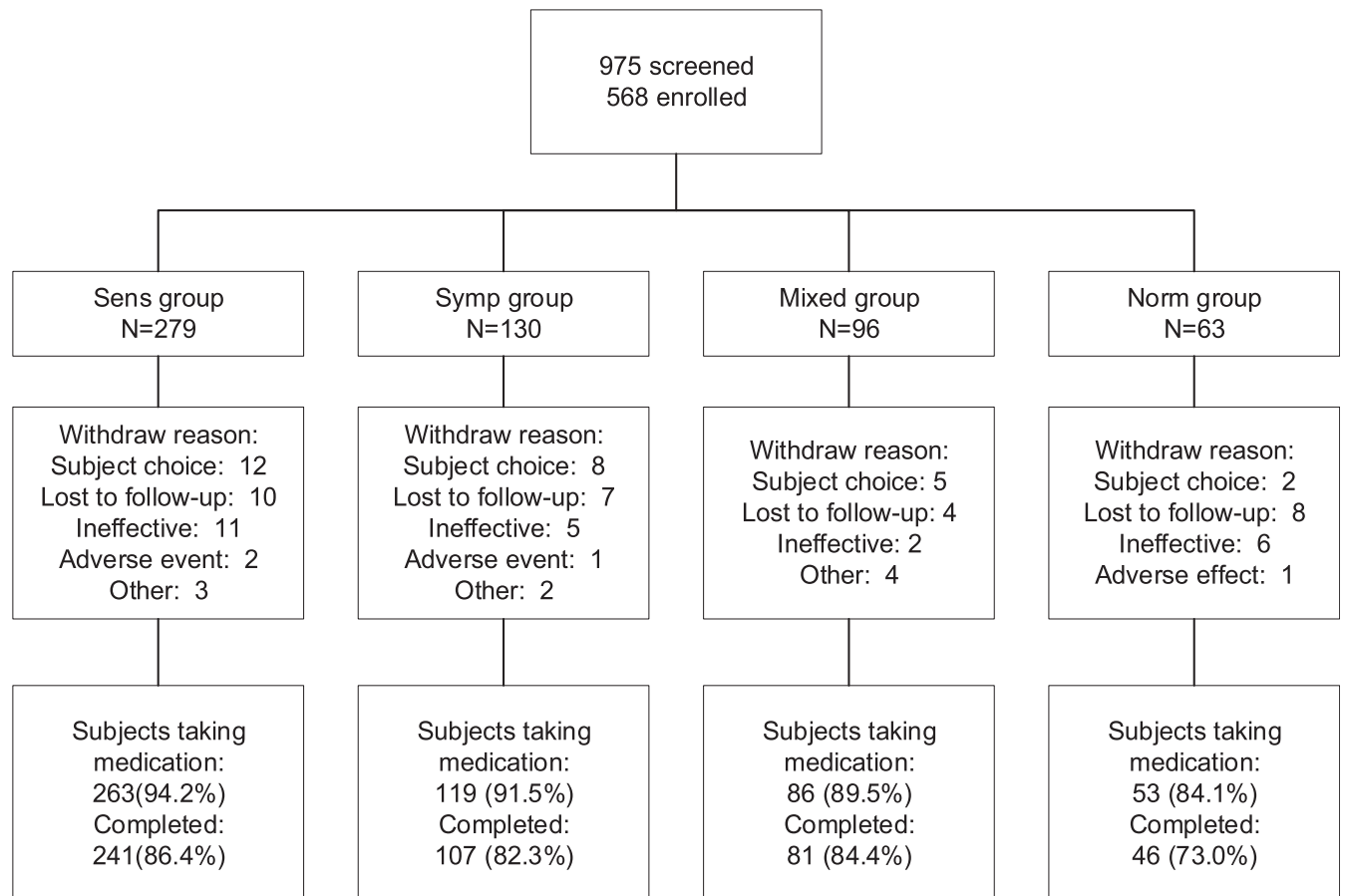


Figure 1. Subject disposition. Data from all patients who took medication and reported at least once were used for analysis as intention to treat analysis.

Table 1. Demographics

	Sens	Symp	Mixed	Norm	p Value
No. pts	279	130	96	63	
Mean±SD yrs age	31.76±10.43	30.91±9.65	29.77±5.01	31.06±6.86	0.320
Mean±SD cm ht	172.97±5.42	173.51±4.91	172.04±5.77	174.05±3.89	0.076
Mean±SD kg wt	70.73±10.75	72.56±13.57	69.29±12	70.35±5.93	0.182
No. married (%)	191 (68.5)	90 (69.2)	61 (63.5)	51 (82.3)	0.078
No. job type (%):					0.215
Physical labor	97 (34.8)	48 (36.9)	32 (33.3)	14 (22.2)	
Brain work	182 (65.2)	82 (63.1)	64 (66.7)	49 (77.8)	
No. \$ income per mo (%):					0.207
<700	190 (68.1)	85 (65.4)	58 (60.4)	48 (77.4)	
700–1,500	78 (28.0)	43 (33.1)	27 (28.1)	12 (19.4)	
>1,500	11 (3.9)	2 (1.5)	5 (5.2)	1 (1.6)	
No. mins self-estimated IELT (%):					0.135
0–0.5	60 (21.5)	27 (20.8)	21 (21.9)	10 (15.9)	
0.6–1	98 (35.1)	42 (32.3)	35 (36.4)	34 (54.0)	
1.1–2	121 (43.4)	61 (46.9)	40 (41.7)	19 (30.2)	
Mean±SD PEDT score	13.01±3.59	13.2±3.23	14.03±3.27	13.37±3.63	0.096
Mean±SD CIPE score	10.54±3.57	11.11±3.33	10.09±3.11	9.84±3.38	0.048
No. PEP outcomes (%):					
Perceived control over ejaculation:					
0 (very poor)	133 (47.7)	60 (46.2)	54 (56.3)	26 (41.3)	
1 (poor)	99 (35.5)	60 (46.2)	33 (34.4)	34 (54.0)	
2 (fair)	44 (15.8)	10 (7.7)	9 (9.4)	2 (3.2)	
3 (good)	3 (7.7)	0	0	1 (1.6)	
4 (very good)	0	0	0	0	
Satisfaction with intercourse:					
0 (very poor)	108 (38.7)	45 (34.6)	39 (40.6)	23 (36.5)	
1 (poor)	119 (42.7)	58 (44.6)	43 (44.8)	35 (55.6)	
2 (fair)	47 (16.8)	25 (19.2)	12 (12.5)	3 (4.8)	
3 (good)	5 (1.8)	2 (1.5)	2 (2.1)	2 (3.2)	
4 (very good)	0	0	0	0	
Personal distress related to ejaculation:					
0 (not at all)	3 (1.1)	1 (0.8)	7 (7.3)	1 (1.6)	
1 (a little bit)	35 (12.5)	11 (8.5)	14 (14.6)	4 (6.3)	
2 (moderately)	53 (19.0)	34 (26.2)	46 (47.9)	9 (14.3)	
3 (quite a bit)	127 (45.5)	62 (47.7)	29 (30.2)	29 (46.0)	
4 (extremely)	61 (21.9)	22 (16.9)	29 (30.2)	20 (31.7)	
Interpersonal difficulty related to ejaculation:					
0 (not at all)	21 (7.5)	6 (4.6)	3 (3.1)	2 (3.2)	
1 (a little bit)	62 (22.2)	30 (23.1)	19 (19.8)	15 (23.8)	
2 (moderately)	70 (25.1)	39 (30.0)	27 (28.1)	13 (20.6)	
3 (quite a bit)	82 (29.4)	45 (34.6)	35 (36.5)	24 (38.1)	
4 (extremely)	44 (15.8)	10 (7.7)	12 (12.5)	9 (14.3)	
Mean±SD ms neurophysiological tests:					
Latency of GPSEP	39.66±2.59	43.76±2.4	39.65±2.86	44.55±2.35	<0.001
Latency of DNSEP	37.93±2.26	41.39±3.81	38.71±2.47	42.34±2.15	<0.001
Latency of PSSR	1,416.56±146.17	1,084.09±118.38	1,086.51±100.13	1,417.82±140.81	<0.001

(Sens and Symp) compared to previously reported effectiveness rates of lidocaine cream and dapoxetine among lifelong PE patients (74%⁶ and 31%,⁷ respectively). All analyses were performed with SPSS 24.0 (SPSS, Chicago, Illinois). Continuous variables were reported as mean±standard deviation, and discrete variables as number (%). One-way ANOVA was used to compare patient characteristics including height and weight, and the total scores of PEDT and CIPE among groups, while the Kruskal-Wallis H test was used to compare the proportion of outcomes among groups, including the proportion of increased IELT and patient-reported outcomes. Repeated measures ANOVA was used to compare IELT at all visits among groups.

Geometric mean IELT (post-hoc) was calculated as the *n*th root of the product of all IELT measurements, where *n* is the number of IELT measurements. The geometric mean was obtained by first computing the arithmetic

mean of the logarithmically transformed values of IELT measurements, and then values were returned to the original scale using exponentiation.

RESULTS

Clinical Characteristics

From October 2015 to July 2017, 975 PE patients were screened and met the inclusion criteria. A total of 568 qualified patients were enrolled in the trial with 475 (83.6%) participants completing the study (fig. 1). Intention to treat analysis was conducted for patients who dropped out due to poor efficacy of treatment or personal reasons. Partial or complete data were obtained from 516 patients (table 1). Missing data resulted from lack of reporting by the subjects (9.15%).

Intravaginal Ejaculatory Latency Time

In the 516 patients who partially or totally completed the study, 427 (82.7%) reported an IELT >2 minutes, and 396 (76.7%) achieved IELT \geq 5 minutes. Among the 462 patients with abnormal electrophysiological test results (Sens, Symp and Mixed group), 401 (86.6%) patients had improved IELT over 2 minutes after the 12-week treatment course, with 396 (85.7%) achieving IELT \geq 3 minutes and 375 (81.0%) achieving IELT \geq 5 minutes. Improvements in IELT were higher than in previous studies of LAs and dapoxetine, which report 74% achieving IELT >2 minutes with LAs⁶ and 29% (30 mg) and 31% (60 mg) achieving IELT \geq 3 minutes with dapoxetine.⁷

For each group, the ratio of patients achieving IELT >2 minutes after treatment was higher in the Sens, Symp and Mixed groups compared with the Norm group ($p < 0.05$; fig. 2, A). The geometric mean of IELT increased from baseline in all groups, but increases were greater in the Sens, Symp and Mixed groups compared with the Norm group ($p < 0.001$; fig. 2, B). Among men with different levels of baseline IELT, the geometric mean IELT and the ratio of men achieving IELT >2 minutes at the week 12 end point were greater in the Sens, Symp and Mixed groups than that of the Norm group (table 2).

Patient-Reported Outcomes

All PEP measures improved in each group after 4–8 weeks of treatment ($p < 0.05$) and persisted up to the week 12 end point (fig. 3). Both improvements from baseline and the percentage of patients with 1-category increase in each PEP measures were not significantly different among the Sens, Symp and Mixed groups, but all were greater than that of the Norm group (table 2). Among CGI-C measures, more patients rated “better” or “much better” in the Sens (83.5%), Symp (86.2%) and Mixed (88.4%) groups than in the Norm group (50.9%). PEDT and CIPE score increased in each group at the week 12 end point from baseline, and the percentage of patients with PEDT and CIPE score increases was higher in the Sens, Symp and Mixed groups compared with the Norm group (fig. 4).

Side Effects

Among patients using compound lidocaine cream, 19 (4.57%) reported erectile dysfunction. No other side effects were reported. Among patients used dapoxetine, 12 (4.52%) reported dizziness, 15 (5.66%) reported nausea or vomiting, 9 (3.39%) reported fatigue, and 1 (0.38%) reported heart palpitations.

Neurophysiological Test Results

After 12 weeks, GPSEP and DNSEP latency increased in the Sens and Mixed groups among

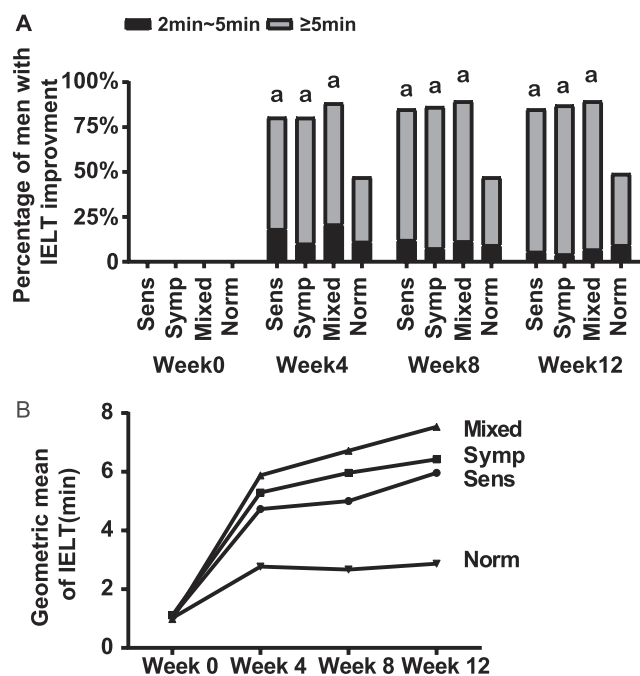


Figure 2. Improvement of IELT and percentage of men with improved IELT over time. *A*, percentage of men achieving IELT >2 minutes and IELT \geq 5 minutes after treatment. *B*, mean average IELT over time. *a*, $p < 0.05$ compared with Norm group.

patients who used compound lidocaine cream, while PSSR latency increased in the Symp and Mixed groups among patients who used dapoxetine. There were no observed changes in latency of neurophysiological tests among the Norm group (fig. 5).

DISCUSSION

In this study, the efficacy of pharmacological treatment strategies based on a novel classification using neurophysiological tests was assessed in lifelong PE patients. In patients with one of the 3 subtypes of neurophysiological abnormalities, tailored treatment with LAs and/or dapoxetine showed a promising improvement in efficacy compared to previous studies.

Classically, PE has been classified according to the timing of the onset of symptoms. In 2008 Waldinger further divided PE as 4 types: primary PE, secondary PE, natural variable PE, and premature-like ejaculatory dysfunction, recognizing underlying pathophysiology and etiology should dictate treatment.¹⁴ In 2013, the International Society of Sexual Medicine adopted their current definition of PE to include lifelong and acquired PE based on the symptoms and subjective feelings of patients.² However, these definitions do not encompass recent developments regarding the neurophysiology of this disorder.

Table 2. Outcomes in men with baseline IELT of ≤ 0.5 minute, ≤ 1 minute, and ≤ 2 minutes

Outcome Measurement	Group Baseline IELT ≤ 0.5 min				Group Baseline IELT ≤ 1 min				Group Baseline IELT ≤ 2 min (overall)				
	Sens	Symp	Mixed	Norm	Sens	Symp	Mixed	Norm	Sens	Symp	Mixed	Norm	
Arithmetic mean IELT:													
No. at baseline	60	27	21	10	158	69	56	44	279	130	96	63	
Mean (SD) at baseline	0.31 (0.20)	0.29 (0.19)	0.25 (0.20)	0.28 (0.18)	0.78 (0.35)	0.69 (0.36)	0.70 (0.38)	0.83 (0.35)	1.23 (0.66)	1.26 (0.68)	1.17 (0.66)	1.18 (0.60)	
No.	56	24	18	7	151	62	51	37	261	116	86	53	
Mean (SD) at wk 12	6.48 (4.09)	7.75 (5.51)	7.72 (3.04)	2.57 (1.51)	6.95 (4.56)	7.56 (4.65)	8.37 (4.18)	4.40 (4.50)	7.40 (4.47)	7.59 (4.28)	8.91 (4.79)	4.37 (4.52)	
p Value vs Norm	0.135	0.031	0.043	-	0.014	0.005	<0.001	-	<0.001	<0.001	<0.001	-	
Achieved IELT more than 2 mins at wk 12:													
Total No.	56	24	18	7	151	62	51	37	261	116	86	53	
No. (%)	49 (87.5)	20 (83.3)	16 (88.9)	3 (42.9)	124 (82.1)	54 (87.1)	45 (88.2)	19 (51.4)	222 (85.1)	102 (87.9)	77 (89.5)	26 (49.1)	
p Value vs Norm	0.016	0.065	0.031	-	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001	-	
Achieved IELT more than 5 mins at wk 12:													
Total No.	56	24	18	7	151	62	51	37	261	116	86	53	
No. (%)	44 (78.6)	20 (83.3)	15 (88.9)	1 (14.3)	111 (73.5)	51 (82.3)	41 (80.4)	15 (40.5)	207 (79.3)	97 (83.6)	71 (82.6)	21 (39.6)	
p Value vs Norm	<0.001	0.001	0.001	-	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001	-	
Geometric mean IELT at baseline and wk 12:*													
No.	44	16	14	4	123	52	46	23	230	104	79	34	
Mean (SE) at baseline	0.36 (1.08)	0.32 (1.13)	0.27 (1.20)	0.2 (1.19)	0.68 (1.05)	0.67 (1.08)	0.65 (1.11)	0.75 (1.14)	1.1 (1.05)	1.13 (1.07)	1.01 (1.09)	1.03 (1.13)	
Mean (SE) at wk 12	6.79 (1.07)	8.51 (1.13)	6.7 (1.17)	2.99 (1.27)	7.18 (1.05)	7.31 (1.08)	7.32 (1.10)	5.13 (1.15)	7.18 (1.04)	7.15 (1.05)	7.92 (1.07)	4.86 (1.13)	
p Value vs Norm	0.010	0.001	0.026	-	0.003	0.001	<0.001	-	<0.001	<0.001	<0.001	-	
Achieved ≥ 1 -category increase in ejaculatory control at wk 12:													
Total No.	56	24	18	7	151	62	51	37	261	116	86	53	
No. (%)	49 (87.5)	21 (87.5)	15 (83.3)	1 (14.3)	119 (78.8)	52 (83.9)	45 (88.2)	17 (45.9)	209 (80.1)	98 (84.5)	73 (84.9)	24 (45.3)	
p Value vs Norm	0.002	<0.001	0.001	-	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001	-	
Achieved ≥ 1 -category increase in satisfaction with sexual intercourse at wk 12:													
Total No.	56	24	18	7	151	62	51	37	261	116	86	53	
No. (%)	48 (85.7)	19 (79.2)	15 (83.3)	2 (28.6)	119 (78.8)	49 (79.0)	43 (84.3)	17 (45.9)	207 (79.3)	91 (78.4)	70 (81.4)	24 (45.3)	
p Value vs Norm	0.002	0.020	0.013	-	<0.001	0.001	<0.001	-	<0.001	<0.001	<0.001	-	
Achieved ≥ 1 -category decrease in personal distress related to ejaculation at wk 12:													
Total No.	56	24	18	7	151	62	51	37	261	116	86	53	
No. (%)	44 (78.6)	19 (79.2)	14 (77.8)	2 (28.6)	115 (76.2)	49 (79.0)	43 (84.3)	19 (51.4)	189 (72.4)	89 (76.7)	74 (86.0)	28 (52.8)	
p Value vs Norm	0.024	0.040	0.065	-	0.011	0.013	0.003	-	0.016	<0.001	<0.001	-	
Achieved ≥ 1 -category decrease in interpersonal difficulty related to ejaculation at wk 12:													
Total No.	56	24	18	7	151	62	51	37	261	116	86	53	
No. (%)	41 (73.2)	20 (83.3)	11 (61.1)	2 (28.6)	97 (64.2)	40 (64.5)	34 (66.7)	13 (35.1)	165 (63.2)	69 (59.5)	63 (73.3)	21 (39.6)	
p Value vs Norm	0.017	0.005	0.144	-	0.007	0.023	0.017	-	0.008	0.083	<0.001	-	

(continued)

Table 2. (continued)

Outcome Measurement	Group Baseline IELT ≤0.5 min				Group Baseline IELT ≤1 min				Group Baseline IELT ≤2 min (overall)			
	Sens	Symp	Mixed	Norm	Sens	Symp	Mixed	Norm	Sens	Symp	Mixed	Norm
Achieved PDET score increase at wk 12:												
Total No.	52	23	18	6	138	57	48	31	241	107	80	46
No. (%)	47 (90.4)	20 (87.0)	15 (88.2)	0 (0)	117 (84.8)	51 (89.5)	43 (89.6)	15 (48.4)	205 (85.1)	96 (89.7)	73 (91.3)	21 (45.7)
p Value vs Norm	<0.001	<0.001	<0.001	.	<0.001	<0.001	<0.001	.	<0.001	<0.001	<0.001	.
Achieved CIPE score increase at wk 12:												
Total No.	52	23	18	6	138	57	48	31	241	107	80	46
No. (%)	44 (84.6)	22 (87.0)	15 (88.2)	4 (66.7)	123 (89.1)	52 (91.2)	45 (93.8)	22 (71.0)	218 (90.5)	97 (90.7)	75 (93.8)	33 (71.7)
p Value vs Norm†	0.027	0.029	0.013	.	<0.001	<0.001	<0.001	.
Achieved CGI-C rating of "better" or "much better" at wk 12:												
Total No.	56	23	18	7	151	62	51	37	261	116	86	53
No. (%)	49 (87.5)	20 (87.0)	16 (88.9)	2 (28.6)	122 (80.8)	53 (85.5)	46 (90.2)	20 (54.1)	218 (83.5)	100 (86.2)	76 (88.4)	27 (50.9)
p Value vs Norm	<0.001	0.002	0.002	.	0.002	0.001	<0.001	.	<0.001	<0.001	<0.001	.

* Subjects with IELT = 0 were excluded when calculating geometric mean.

† No significance by Kruskal-Wallis test.

The DNSEP is an electroencephalographic measurement of cortical activity in response to an evoked potential of the somatosensory area of the penile dorsal nerve. The GPSEP is similar to DNSEP but involves stimulation of the glans penis.⁸ In our study, patients with shortened latency of SEPs saw greater improvement in IELT with LAs, indicating SEP latency may be a reliable parameter in assessing the likelihood of treatment success with LAs. The SSR is a commonly used functional test of the sympathetic nervous system to assess small fiber function and is frequently used in diagnosis of thin, unmyelinated fiber lesions in diabetic neuropathy and uremic neuropathy in clinical neurological practice.¹⁵ In previous studies, we found that N-methyl-D-aspartic acid (NMDA)¹⁶ and gamma-aminobutyric acid (GABA) receptors¹⁷ were involved in the regulation of ejaculatory behavior in rats via sympathetic outflow. Further studies are needed to elucidate the neuropathological mechanisms of PE and the correlation with sympathetic function.

To our knowledge, this is the first study proposing a classification of PE based on neurophysiological testing. The results of this study offer new treatment strategies for PE based on proposed neurological mechanisms of the disorder. Patients with abnormal results of neurophysiological tests had improved efficacy with LA and/or dapoxetine, indicating personalized treatment may be superior in management of PE. Further investigations are needed to explore PE treatment strategies in relation to sensory and sympathetic latency instead of empirical treatment. Additional research is warranted to evaluate behavioral and surgical management in relation to this method of classification.

There are several limitations in this study. This trial was nonrandomization and lacked placebo groups. Study participants were limited to the Chinese in Jiangsu province. Only lifelong PE patients were enrolled in this trial, thus it is unknown if the classification system and treatment strategies fit for acquired PE patients. To avoid affecting the mood of sexual intercourse by using the stopwatch, we used the self-estimated IELT. PEDT, CIPE and CGI-C questionnaires were set to be filled at the last visit. For patients lost to followup, PEDT, CIPE and CGI-C data were incomplete. Patients who elected to leave the trial were encouraged to attend a final visit and complete all questionnaires. If patients were unwilling to undergo a clinic visit, the CGI-C questionnaire was elicited through a phone call. The dropout rate of the study was higher than 10%, which may compromise the results of the study. The sample size was miscalculated before the enrollment of patients, leading to an insufficient sample size for group Symp with post hoc power at 75.0%

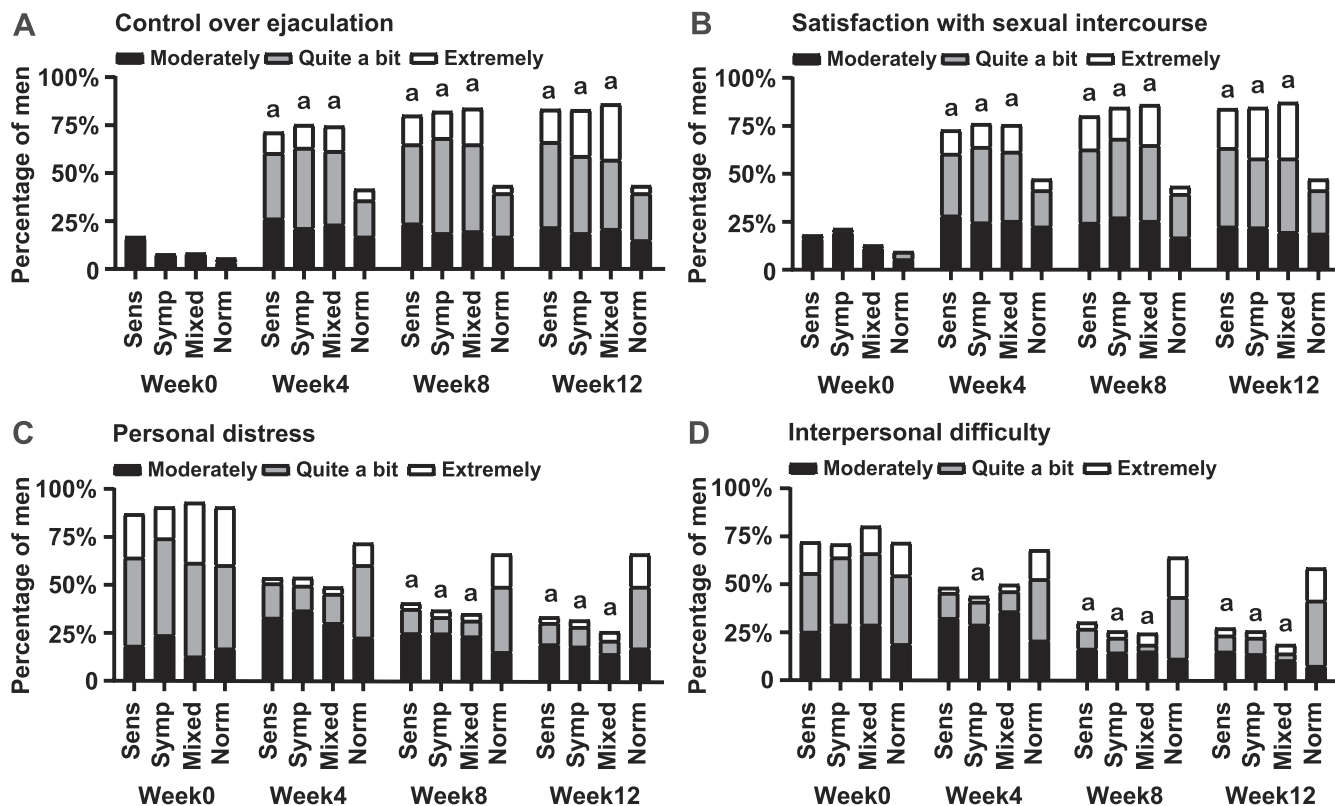


Figure 3. PEP change over time. *A*, control over ejaculation. *B*, satisfaction with sexual intercourse. *C*, personal distress. *D*, interpersonal difficulty. *a*, $p < 0.05$ compared with Norm group.

(99% for group Sens). Thus more patients with abnormal PSSR results are necessary in future studies. As there are no previous data stating the efficacy of combination of LAs and dapoxetine on LPE, the sample size of the groups Mixed and Norm were not calculated.

common treatments for the disorder. Our results demonstrate increased efficacy of LAs and dapoxetine among patients with hyperexcitable somatosensory and sympathetic latency. Further studies are needed to validate this classification in diagnosing and treating PE.

CONCLUSIONS

This study presents a novel classification of PE with proposed treatment strategies using the 2 most

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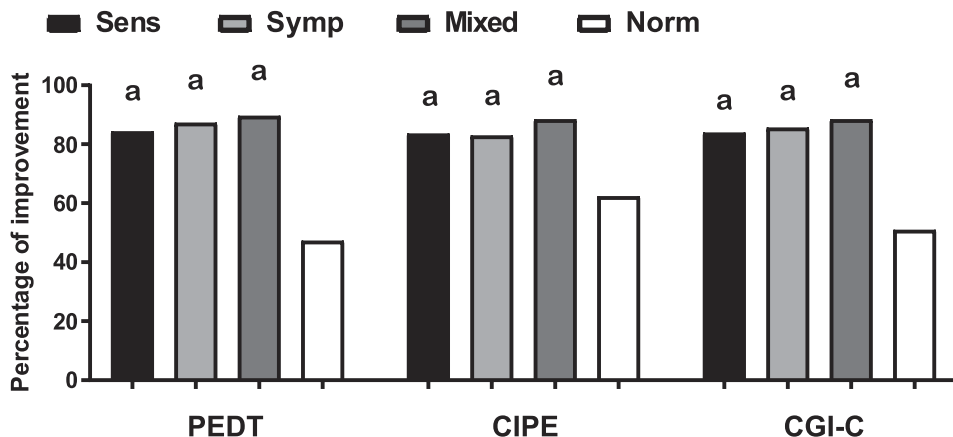


Figure 4. Proportion of patients with improved score of PEDT, CIPE and CGI-C. *a*, $p < 0.05$ compared with Norm group.

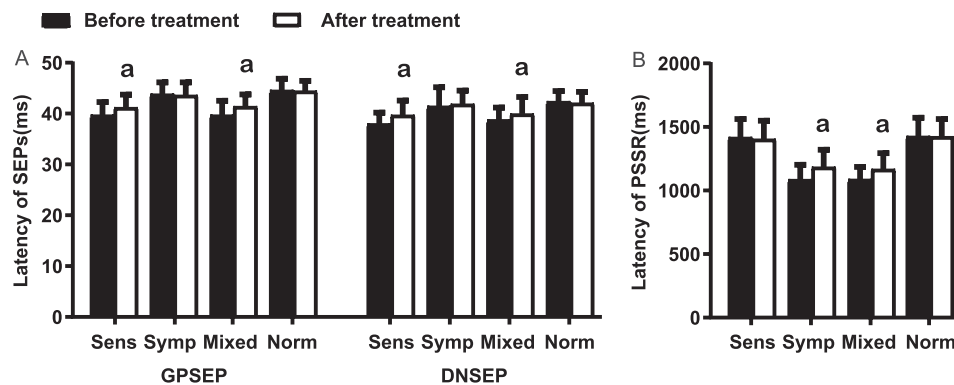


Figure 5. Neurophysiological test results. A, SEPs. B, PSSR. a, $p < 0.05$ compared with Norm group.

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EDITORIAL COMMENT

This paper describes a novel way of approaching premature ejaculation (PE). The concept and findings are provocative in that this new classification system based on neurophysiological testing could be clinically relevant and provides something novel in the management of PE. The main objective is to test the

hypothesis that targeted treatment based on specific neurophysiological tests for PE is more efficacious. Until today, we do not fully understand the etiology of PE, and we do not have objective tools for diagnosis and no individualized therapy for management.¹ The results support their hypothesis; however, there are a

number of limitations that will likely hinder its translation to current clinical practice.

The biggest limitation to this study is the validity of the neurophysiological tests used to classify patients to one of the 4 PE treatment groups. These same 4 classifications are based on studies by the same group that include a small number of patients and hasn't been replicated or externally validated (references 8 through 10 in article). Also, bear in mind that the design of the current study is not a randomized placebo-controlled study. One of the main outcome measures is self-estimated intra-vaginal ejaculation latency time (IELT), whereas most high-quality studies have used a stopwatch, controlled by the partner, to accurately measure the improvement of IELT after intervention. However, the authors did use the Premature Ejaculation

Profile (PEP) questionnaire, which is arguably a better patient-centered outcome measure.

Patients with sensory, sympathetic and mixed hyperexcitability improved significantly with their targeted treatment. Patients with "normal type" PE also reported improvement up to 50% with the treatment, although significantly less than the groups with presumably an identifiable etiology. Again, while the results are intriguing, a further designed study with appropriate power calculation and control group, in addition to external validation, are in order before implementing the results of this study into clinical practice.

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