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From Waterloo to the Great Wall: A retrospective, multicenter study on the clinical practice and cultural attitudes in the management of premature ejaculation, in China

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Premature ejaculation (PE), despite its wide prevalence, is largely underdiagnosed and undertreated. Being a multifactorial dysfunction with strong cultural characteristics, PE requires skillful attitudes in the psychosexological support, necessary to manage the patient's and the couple's expectations, as well as in the medical treatment. Dapoxetine is a short-acting selective serotonin reuptake inhibitor approved for use in lifelong and acquired PE in a number of countries. Opinions, not always generated by the evidence-based medicine, impacted the attitudes of Western andrologists, as a nocebo

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effect which produced a drug's Waterloo, characterized by low prescription rates much more built on the patients' and doctors' expectations than on costs, side effects, and efficacy.

In the present study, we retrospectively reviewed real-life data from eight Andrology and Sexual Medicine Public Centers in China to assess the prevalence of PE among attending patients, its association with erectile dysfunction, its subtype, and the proposed treatments. In 2019, among 156,486 patients coming to the centers, 32,667 visits having PE as the chief complaint were performed (20.9%). Almost all patients received treatment prescriptions (32,641 patients, 99.92%); 23,273 patients came back for a follow-up visit in the subsequent 12 months (71.2% of those who initially received treatment). Dapoxetine, either alone or in combination with another therapy, was the most prevalent treatment, prescribed to 22,767 patients (69.7% of treated patients), followed by traditional Chinese medicine (TCM) (39.4%). At follow-up, 8174 patients were unsatisfied with treatment, and a new treatment was proposed (35.12%). Dapoxetine was the best treatment, with an overall 27.1% switching rate when used either alone or in combination: Although the switching rate for Dapoxetine alone was 44.2%, the association of the same drug with psychotherapy resulted in much lower rates (19.5%) and reached a minimum of 12% when also combined with TCM demonstrating how cultural aspects and medical attitudes may dramatically impact on the therapy of a multifaceted, complex, and culture-grounded sexual symptom such as PE.

In conclusion, taking switching rates as surrogate markers of treatment failure, this real-life study—the largest in the field—shows that in a more patient-oriented (as in Chinese medical culture), and less symptom-oriented (as in Western medical attitudes), Dapoxetine is a successful treatment for PE patients, with higher reliability when used alone or as part of combined and integrated therapies.

KEYWORDS
dapoxetine, premature ejaculation, SSRI, traditional Chinese medicine, treatment

1 | INTRODUCTION

Although the field of erectile dysfunction (ED) and related guidelines is pigeonholed in a substantial uniformity and homogeneity of the evidence and positions[1–3] (with relatively little debate on the use of old, such as surgery, and new, such as shockwaves therapies[4,5]), that one of premature ejaculation (PE) results characterized by the admission that the main pathophysiological mechanisms, the diagnostic workups, and managements are not universally accepted.[6–8] This is also clearly demonstrated by the mono-dimensional definition of the former[9] (inability to reach/maintain erection), facing a tri-dimensional definition of the latter[7] (loss of control on the ejaculatory mechanism, stress-induced/inducing, and short time from penetration to ejaculation).[10] For example, the neurobiological hypothesis on a genetic involvement of the serotoninergic pathway on lifelong forms of PE (LPE), although popular in the last 20 years, has been found confirmed in rodents (animals with a peculiar copulatory behavior and penile anatomy),[11] but never, with robust findings, in humans, whereas in the patient's clinical history, both sexual symptoms are bona fide anticipated by subclinical forms[12,13] (surprisingly not too frequently explored[14]), PE appears as more multifaced than ED.[6,7]

For a long time, PE has been considered merely a psychorelational sexual dysfunction to be exclusively treated by psychotherapies,[15] until the revolutionary proposal of the Dutch psychiatrist Marcel Waldinger to therapeutically exploit the common anti-ejaculatory side effects of the serotoninergic antidepressants in the management of PE.[16] Although this genial intuition opened a huge highway of investigations,[17] improving the sexual health of a large number of patients, it produced the erroneous scientific perception that the patients with PE must have a serotoninergic central derangement, leading to ineffectual research. In these regards, the idea that PE could be generated by an impaired, absolute or relative, serotoninergic activity, possibly genetic in nature,[18] has been used to justify the use of serotoninergic drugs in the PE treatment. However, exactly as in ED

patients, the symptom can be resolved by inhibiting PDE5, in subjects with PE the symptom can be overcome by increasing the presence of the serotonin in the synaptic cleft. But this simple evidence seems not as easy to be accepted by a number of researchers still looking for a neurobiological/morphological alteration in PE.[19]

In fact, the chapter of PE therapy is still under debate. Again, although PDE5 inhibitors are universally accepted for ED therapy,[20] there definitely is no "one-size-fits-all" strategy for the management of PE. Some forms of PE, most frequently included among acquired forms of PE (APE), can successfully be treated by administering specific treatments, such as thyrostatic drugs for patients diagnosed with hyperthyroidism[3,6,21–23] or anti-inflammatory/antibiotic therapies for patients diagnosed with prostatitis.[23–26] However, a definite, treatable organic factor for PE is rarely identified, leading to the widespread, abovementioned idea that PE is mostly "psychogenic" in nature. Although it is in fact undeniable that PE is often associated with performance anxiety,[3,27,28] in the broader context of the "loss of control of erection and ejaculation" (LCEE),[13] as well as in patients with poor psychological health,[29,30] it should be considered that the biological mechanisms regulating ejaculation are obviously organic in nature: Therefore, the multifactorial origin of PE should always be considered during the diagnostic and therapeutic process.[15,31] Therefore, current guidelines suggest providing both psychosexological support and medical treatment for PE.[3,6,8] Unsurprisingly, some patients report beneficial outcomes in terms of ejaculatory latency when using PDE5 inhibitors: Indeed, such drugs can potentially improve the sense of control over performance anxiety in some patients. The concept of LCEE provides a clear explanation of the efficacy of these treatments: Each sexual dysfunction can potentially contribute to the onset or worsening of the other, and therefore, acting on either one can also have beneficial effects on the other.[13,32]

A fundamental milestone in the history of PE was the development and marketing in several countries of a short-acting selective serotonin reuptake inhibitor (SSRI) derived from fluoxetine,[33] named Dapoxetine.[34] The drug was approved by several medical agencies not as an antidepressant, being exempt from mood-regulating effects owing to its very short half-life which prevents accumulation,[35] but as the first (and so far unique) oral treatment for PE. Dapoxetine is now recognized as the gold standard of the medical treatments for both LPE and APE,[36] whereas local anesthetics have been more recently approved for use only in the case of LPE.[37,38] Apparently, all PE treatments, however, are burdened with varying degrees of efficacy and high discontinuation rates, also owing to their costs and posology, and patient's expectations.[39,40] In fact, for a number of reasons, interesting to explore and to study in deep, despite excellent clinical outcomes in randomized controlled trials,[41,42] in Western Countries, the prescriptions of the new short-acting SSRI have been so low that the scenario has been depicted as the "Waterloo" of the Dapoxetine.[43] However, the perception of a low efficacy of the drug, relatively diffused in the Western urological milieu on the basis of opinions and not on published and controlled evidence,[44,45] was not universal. In oriental countries, such as China or Vietnam, the use of Dapoxetine has been much more successful, and it is currently much largely diffused than in Europe or in other Western countries.[46–48] The dose-dependent efficacy in the three dimensions of PE (increasing the feeling of control on ejaculatory mechanisms, reducing the distress produced by PE, as measured by well validated psychometric tools exploring patient reported outcomes, and the increase in the intravaginal ejaculatory latency time [IELT], as measured by the stopwatch)[49] does not justify the low prescription rate in Western doctors. Similarly, the Waterloo scenario appears not justified by the Dapoxetine safety profile, which is much more tolerable than all other SSRIs, frequently prescribed off-label for PE.[50] In the Waterloo effect, cultural factors and doctors' opinions may have played and may still play a major role. For example, it has been claimed that the majority of a small number of Dutch patients with LPE prefer daily treatment with high-risk SSRIs with respect to on-demand treatment with a better risk/benefit ratio.[51] This is surprising also considering the large number of SSRI-induced side effects but also considering the possibility of a severe post-SSRI sexual disease described after chronic use of this drug class, but never in Dapoxetine users.[52–54]

On the basis of this complex background, in the present study, we retrospectively reviewed data from several Chinese centers active in PE management in order to highlight culturally driven clinical behaviors and to measure, by means of follow-up and treatment switch rates, to what extent different treatments were considered reliable by doctors and patients, and by extension, the prevalence of PE, its duration (LPE vs. APE) and its association with ED, as in the LCEE.

2 | MATERIALS AND METHODS

2.1 | Survey design

A letter and blank survey were sent to 10 major centers in China describing the project and requesting their participation. Centers have been selected as active in basic and clinical research on PE and participating to international meetings of sexual medicine and andrology. They do not represent the whole Chinese scientific community in the field, but a large part of it, and are all located East of the "Heihe–Tengchong Line," that is, in the area where 94% of China's population live. Among participating centers, only two are mainly traditional Chinese medicine (TCM)-oriented, namely, the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine and the Beijing Xiyuan Hospital of the China Academy of Chinese Medical Sciences.

The main objective was to carry out a real-life retrospective, multicenter survey on the prevalence of PE and on the use of different therapies for its treatment in China.

Participants were asked to refer to the International Society of Sexual Medicine (ISSM) definitions of LPE and APE[8] and to the National Institutes of Health definition of ED.[9] Severity of ED was graded as mild, moderate, and severe, using the simplified International Index of Erectile Function (IIEF-5) scores.[55] In terms of statements, "continuous/repetitive" was to be used when the condition occurs ≥25% of times, "non-occasional" between 10% and <25% of times, and "occasional" for <10% of times. Sexological criteria were used to define

TABLE 1 Participating centers

Center name	Overall visits in 2019	PE visits in 2019
Peking University 3rd Hospital	*N* = 50,250 (32.11%)	*n* = 8000 (24.5%)
First Teaching Hospital of Tianjin University of Traditional Chinese Medicine	*N* = 8200 (5.24%)	*n* = 2380 (7.3%)
Xiyuan Hospital of China Academy of Chinese Medical Sciences	*N* = 47,996 (30.67%)	*n* = 10,559 (32.3%)
Shenzhen Key Laboratory of Fertility Regulation	*N* = 1500 (0.96%)	*n* = 360 (1.1%)
First Affiliated Hospital of Anhui Medical University, Hefei	*N* = 37,000 (23.64%)	*n* = 9120 (27.9%)
Xijing Hospital, Fourth Military Medical University, Xi'an	*N* = 2200 (1.41%)	*n* = 736 (2.3%)
3rd Affiliated Hospital of Sun Yat-sen University, Guangzhou	*N* = 7490 (4.79%)	*n* = 1000 (3.1%)
Xi'an Daxing Hospital	*N* = 1850 (1.18%)	*n* = 512 (1.6%)

Abbreviation: PE, premature ejaculation.

subclinical ED (SED), defined as a continuous or repetitive inability to achieve or maintain an erection sufficient for satisfying sexual activity.[12] SED is diagnosed when at least one major and two minor criteria are met (Table S1).

To be included in the study, it was requested that patients have an age of at least 18 years and a diagnosis of PE.

Being the clinical definition of subclinical PE (SPE)[13] not available at the time of the present survey, it was not considered here. However, for the sake of clarity, criteria for diagnosis of SPE have been included as part of the supplementary material (Table S2).

Data from 01.01.2015 to 31.12.2019 were collected, divided by year; where unavailable, centers collected data for a shorter period, always indicating year by year.

2.2 | Statistical analysis

Descriptive statistics were used to summarize pertinent study information. Associations between categorical variables were analyzed according to the Pearson chi-square test. The statistical software R (version 4.1.1, R core team, Vienna, Austria) was used for all analyses. Figure 2 is drawn using SankeyMATIC (www.sankeymatic.com).

3 | RESULTS

Among the 10 invited centers, 9 agreed to participate in the survey, and 8 returned completed questionnaires (Table 1). In all, from the 5-year period from 2015 to 2019, a total of 654,590 patients were seen in the centers actively participating to the survey.

Being the time of clinical activity different from Center to Center, for the present analysis, the data refer to 2019 (January 1–December 31), unless otherwise specified.

In all, the 8 centers reported a total of 156,486 patients observed during the pre-pandemic year 2019 (Figure 1). Of these, 32,667 (20.9%) referred to PE (Figure 2). APE accounted for almost 46.8% of cases and LPE in nearly 36.1%. The remaining cases (17.1%) were undefined or were found ex-post with other complaints related to the lack of control of ejaculation.

TABLE 2 Prevalence of premature ejaculation (PE) in combination with different forms of erectile dysfunction (ED)

Type	%
No ED	34.6
Comorbid ED + PE	65.4
PE + subclinical ED[a]	24.3
PE + mild ED	35.7
PE + moderate ED	23.6
PE + severe ED	16.3

[a]Data on subclinical ED[12] available from six centers only.

The association of ED in combination with PE, later defined as LCEE, was also addressed (Table 2). Overall, among all patients included in analysis, almost two out of three subjects (65.3%) had comorbid ED of varying severity, and only 34.6% of subjects did not complain of ED. Among subjects having LCEE, most had mild ED (35.7%), and progressively lower rates were found for moderate and severe ED (23.6% and 16.3%, respectively). The remaining 24.3% patients were classified as SED.

In 2019, as stated, 32,667 visits with PE as the chief complaint were performed in the 8 participating centers. A total of 32,641 patients received treatment (99.92%), and 23,273 came back for a follow-up visit in the subsequent 12 months (71.2% of those who initially received treatment). According to the study protocol, patients were treated according to the clinicians' experience, their practice, and their clinical judgment on the patient's needs and requests.

Dapoxetine, either alone or in combination with another therapy, was the treatment of choice in 22,767 patients (69.7% of treated patients). TCM was the second most used treatment, accounting for about 39.4% of all administered treatments (4693 patients treated with TCM alone, and 8176 in combination with Dapoxetine), whereas 15.9% were treated with other treatments, either alone or in combination (Table 3). As shown in Table 4, clinicians in different centers have different treatment approaches to their patients. As an example, Dapoxetine was used in close to 100% of patients in some Western medicine-oriented centers, whereas its prevalence of use was around 20% in other more TCM-oriented centers. Among the 12,869

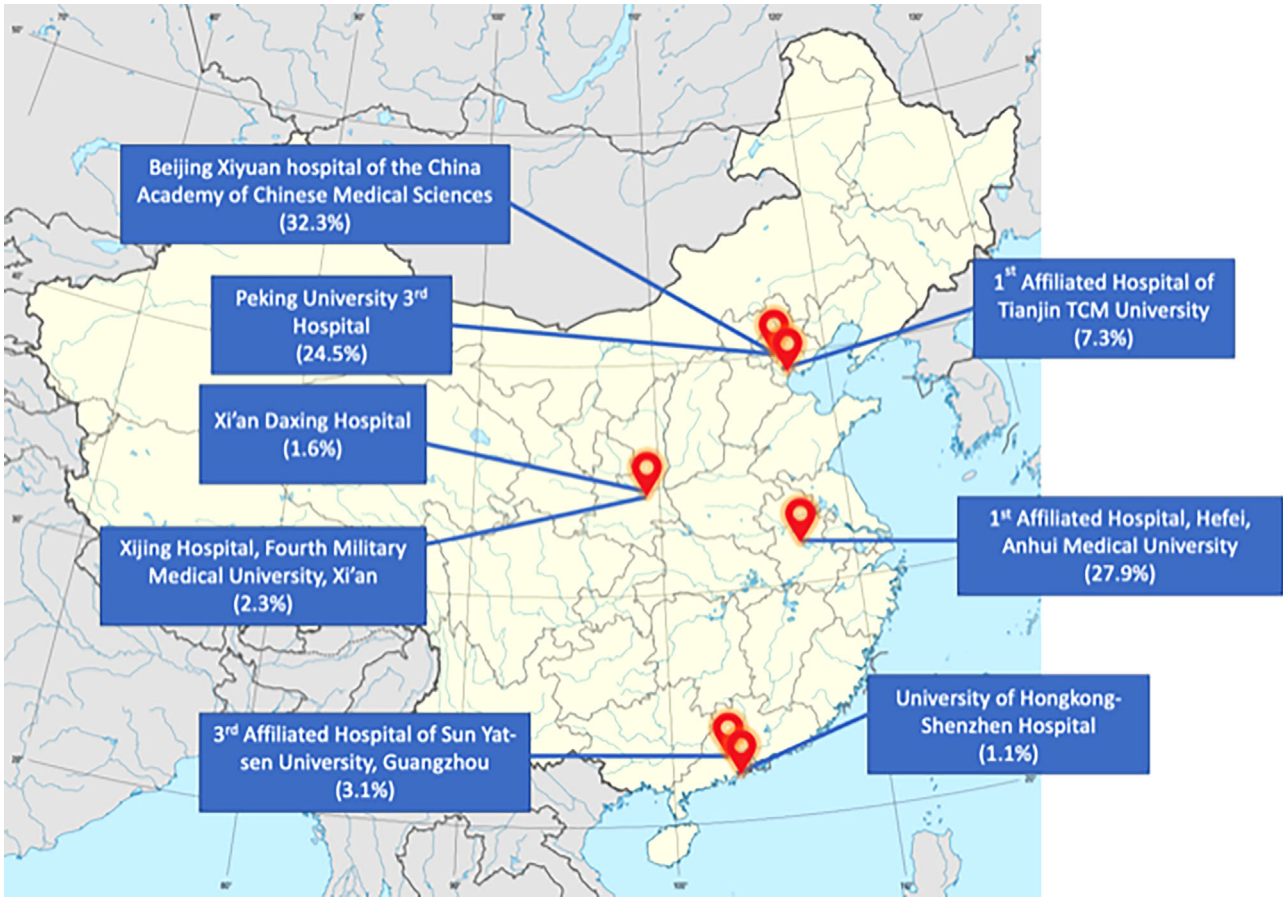

FIGURE 1 Map of China showing the approximate location of all participating centers.

TABLE 3 Treatments administered for premature ejaculation (PE), including follow-up and treatment switch rates

Treatment	Treated ($n = 32,667$)	Follow-up ($n = 23,273$)	Switch ($n = 8174$)
Dapoxetine (all)	22,767 (69.69%)	15,887 (69.78%)	4299 (27.06%)
D. alone	3190 (9.77%)	2162 (67.8%)	955 (44.2%)
D. + psychotherapy	1812 (5.55%)	822 (45.4%)	160 (19.5%)
D. + psychotherapy + local anesthetics	6630 (20.3%)	4607 (69.5%)	1860 (40.4%)
D. + psychotherapy + PDE5i	2959 (9.06%)	1410 (47.7%)	498 (35.3%)
D. + psychotherapy + TCM	8176 (25.03%)	6886 (84.2%)	826 (12%)
Local anesthetics alone	1185 (3.63%)	882 (74.4%)	487 (55.2%)
No treatment	26 (0.08%)	6 (23.1%)	4 (66.7%)
Other combinations without Dapoxetine	1679 (5.14%)	1075 (64%)	554 (51.5%)
Other treatments	55 (0.17%)	55 (100%)	39 (70.9%)
PDE5i alone	755 (2.31%)	330 (43.7%)	223 (67.6%)
Psychotherapy alone	786 (2.41%)	548 (69.7%)	350 (63.9%)
SSRIs or other antidepressants alone	622 (1.9%)	436 (70.1%)	257 (58.9%)
Surgery	99 (0.3%)	73 (73.7%)	57 (78%)
TCM alone	4693 (14.37%)	3981 (84.8%)	1904 (47.8%)

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TCM, traditional Chinese medicine.

TABLE 4 Use of different treatments according to Center

Treatment	Beijing III	Beijing Xiyuan	Guangzhou	Hefei	Shenzhen	Tianjin	Xian Daxing	Xian Xijing
Dapoxetine (all)	6160 (77%)	6524 (61.8%)	1000 (100%)	7200 (78.9%)	300 (83.3%)	1310 (55%)	113 (22.1%)	160 (21.7%)
D. alone	160 (2%)	225 (2.1%)	0 (0%)	1920 (21.1%)	300 (83.3%)	360 (15.1%)	82 (16%)	143 (19.4%)
D. + psychotherapy	800 (10%)	0 (0%)	810 (81%)	0 (0%)	0 (0%)	200 (8.4%)	1 (0.2%)	1 (0.1%)
D. + psychotherapy + local anesthetics	1200 (15%)	0 (0%)	0 (0%)	5280 (57.9%)	0 (0%)	150 (6.3%)	0 (0%)	0 (0%)
D. + psychotherapy + PDE5i	1600 (20%)	869 (8.2%)	190 (19%)	0 (0%)	0 (0%)	300 (12.6%)	0 (0%)	0 (0%)
D. + psychotherapy + TCM	2400 (30%)	5430 (51.4%)	0 (0%)	0 (0%)	0 (0%)	300 (12.6%)	30 (5.9%)	16 (2.2%)
Local anesthetics alone	80 (1%)	55 (0.5%)	0 (0%)	960 (10.5%)	20 (5.6%)	70 (2.9%)	0 (0%)	0 (0%)
No treatment	0 (0%)	26 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other combinations without Dapoxetine	800 (10%)	310 (2.9%)	0 (0%)	0 (0%)	0 (0%)	230 (9.7%)	145 (28.3%)	194 (26.4%)
Other treatments	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	30 (5.9%)	25 (3.4%)
PDE5i alone	400 (5%)	210 (2%)	0 (0%)	0 (0%)	20 (5.6%)	120 (5%)	4 (0.8%)	1 (0.1%)
Psychotherapy alone	160 (2%)	46 (0.4%)	0 (0%)	480 (5.3%)	0 (0%)	100 (4.2%)	0 (0%)	0 (0%)
SSRIs or other antidepressants alone	80 (1%)	38 (0.4%)	0 (0%)	384 (4.2%)	20 (5.6%)	100 (4.2%)	0 (0%)	0 (0%)
Surgery	0 (0%)	0 (0%)	0 (0%)	96 (1.1%)	0 (0%)	0 (0%)	0 (0%)	3 (0.4%)
TCM alone	320 (4%)	3350 (31.7%)	0 (0%)	0 (0%)	0 (0%)	450 (18.9%)	220 (43%)	353 (48%)

Abbreviation: SSRIs, selective serotonin reuptake inhibitors; TCM, traditional Chinese medicine.

FIGURE 2 Prevalence of different subtypes of premature ejaculation (PE) in the study population.

patients being treated with TCM, either alone or in combination, most were followed in the Beijing Xiyuan Hospital of the China Academy of Chinese Medical Sciences (8780 patients, 68.2%) and the Beijing University Third Hospital (2720 patients, 21.1%). The two mainly TCM-oriented centers had significantly lower dropout (1902/12,939 vs. 7508/19,728, $p < 0.001$) and switch rates (3395/11,037 vs. 4795/12,220, $p < 0.001$) rates.

Table 3 and Figure 3 also show the follow-up rates and the switching from one therapy to another, for the specified therapies. Overall, the follow-up rate for all patients coming to the different centers involved was 71.2% (23,273 patients), suggesting that almost 3 out of 10 PE patients are lost to follow-up. Follow-up rates were significantly different among treatments ($p < 0.0001$); most notably, follow-up rates for TCM were remarkably high (84.8%), and likewise the inclusion of TCM in combination therapies was associated with similarly high follow-up rates (84.2%). A treatment switch was prescribed in 8174 patients among those coming at follow-up visits, meaning that slightly more than one out of three patients coming to follow-up was not fully satisfied by the first treatment proposed (35.12%). As for follow-up, the rate of treatment switch was significantly different among centers ($p < 0.0001$). Surgery was the treatment with the highest rates of switching (78%), followed by PDE5i used alone (67.6%) and psychotherapy alone (63.9%). Among patients exclusively treated with TCM, almost half requested a treatment switch (47.8%). The lowest rates of treatment switch were instead found for Dapoxetine: Overall, when considering Dapoxetine alone and in combination, switching rate was about 27.1%. Combination use was more successful than the

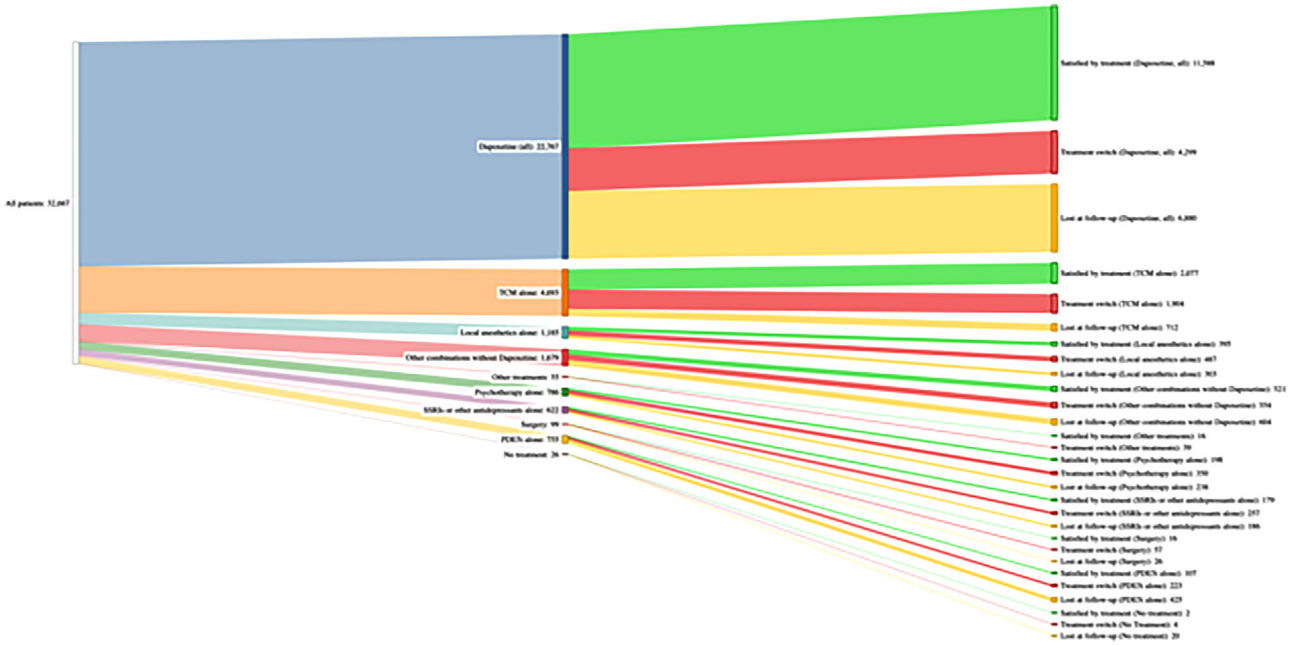

FIGURE 3 Sankey diagram describing treatment flow for the study population. Colors in the rightmost part of the diagram provide a visual representation of the different outcomes of treatment (*green: satisfied with treatment; red: treatment switch necessary; yellow: patient lost at follow-up*).

use of Dapoxetine alone: Indeed, although switching rate for Dapoxetine alone was 44.2%, association of the same drug with psychotherapy resulted in much lower requests for switching (19.5%) and reached a minimum of 12% when also combined with TCM.

4 | DISCUSSION

Although limited by the retrospective design and by the obvious heterogeneity of the clinical behavior of the clinical centers, this is one of the largest real-life studies in the field of PE management.

We found that objective PE (APE + LPE) is one of the more frequent sexual complaints, being present in more than 1 out of 5 patients attending 8 of major Chinese outpatient clinics practicing either Western or TCM. Interestingly, this percentage mirrors other previous epidemiological studies in different countries.[28,56–64] A similar prevalence (28%) has recently been found in a single-center Italian report.[14] Subclinical forms of PE[13] or subjective PE[65] have not been considered in this retrospective study, which is one of the largest strictly based on the ISSM criteria and not on other definitions of PE and PE-like, or subjective, conditions.

Our study focused on follow-up and treatment switch rates in order to show a picture of the clinical behaviors and attitudes in China in the PE management and to have surrogate indications on the efficacy of different available therapies examining the rate of refilling or changes of drugs/treatment in the follow-up. However, to fully evaluate the study outcomes, it is mandatory to consider the "true" meaning of follow-up rates and requests for treatment switch. Patients might be lost at follow-up for a plethora of reasons, which include, but are not limited to, treatment inefficacy (e.g., they moved to another city, they were ill on that day, they were no longer interested in addressing this issue, they forgot, etc.). On the other hand, it could also be quite the opposite: The patient might disregard the follow-up visit because the proposed treatment was perfectly effective, and therefore, subsequent evaluation might not be deemed as necessary as before. Therefore, judging the efficacy of a treatment by the frequency of follow-up visits does not seem, apparently, a viable strategy. On the other hand, it can be assumed that patients who show up at such follow-up visits are the most reliable population upon which to assess treatment efficacy. Those who did not ask for a treatment switch were, most likely, completely satisfied with their prescription; on the other hand, those who found their initial treatment to be inadequate came back asking for a new therapy, for example, as shown by the high rates of switching after initial surgery treatment. Therefore, treatment switch can be considered a surrogate marker for assessing the efficacy of different therapies, even more in the context of real-life studies for conditions such as PE, which are largely underdiagnosed and undertreated.[13,66] PE is a sexual symptom, that is, by definition, largely dependent on sociocultural and relational contexts, and as such, it is largely expected that the efficacy and compliance to treatment are similarly dependent on the same factors. Our study results show that Dapoxetine, when administered either alone or in combination with other treatments, was the most successful treatment for PE in China, owing to the lowest rates of treatment switch requested by patients.

Real-life studies on a large population, such as the present one, prove that the same treatments can have different rates of success in different centers. On a broader scale, our results prove that some treatments, at least in the Chinese population, are unequivocally associated with better follow-up and fewer requests for treatment change. Combination therapy is generally more likely to succeed in

treating PE, acting synergistically on the different factors involved in the pathogenesis of this sexual dysfunction and/or on the patients' expectations. Such factors can possibly explain why Dapoxetine, while potentially being the most "targeted" treatment for management of PE, has had varying rates of success in clinical trials. The clearest example of this comes from an Italian study from 2013, performed on just 120 patients complaining of PE, which showed poor efficacy of Dapoxetine and poor compliance to treatment.[43] Several factors were considered likely culprits of this "Waterloo," including drug costs, side effects, and perceived lack of efficacy. However, as IELT remarkably and significantly increased in subjects deciding to continue treatment, the perceived poor efficacy can also be attributed to doctors' prejudices, inadequate management of expectations, and lack of psychosexological consultations. Studies without any psychosexological assessment, in fact, show remarkably higher treatment discontinuation rates and lower satisfaction.[43,67] This is unsurprising, as perception of any improvement for sexual health could be differently judged according to patient's expectations.[6] A common clinical scenario depicts a patient complaining of LPE, having an IELT of about 1 min since his first sexual experiences, who is able to delay ejaculation for up to 3.5 min while undergoing an effective treatment. The same patient could be satisfied by his more than threefold increase in IELT, but at the same time, his time to ejaculation might be too short to provide enjoyable sexual intercourse for both partners. Undoubtedly, this clinical situation represents a possible target for careful counseling, if not for a tailored sexological treatment, possibly involving the couple rather than the man alone in order to adequately manage the couple's distress and expectations.[6,31] Failing to address this issue can potentially decrease the compliance to treatment, as the therapy itself would be deemed ineffective by the couple,[13] therefore leading to either loss at follow-up or subsequent visits for new treatments. To an extent, likelihood of treatment success can possibly be predicted by the use of nomograms[68]: These nomograms frequently rely upon Clinical Global Impression of Change, rather than on changes to IELT or patient-reported outcomes, in order to provide reliable assessment on treatment efficacy.[69]

Establishing a good doctor–patient relationship is another item to be considered in the management of many conditions, and particularly in the case of PE. Treatment compliance can also be affected by the stigma associated with SSRIs[66,67,70]: In fact, the idea that an antidepressant drug is necessary to treat PE might be misinterpreted by patients, who might be worried about the effects on mental health and behavior of these substances, or who might also be skeptical of their doctor's suggestions. Most SSRIs can impair sexual health,[6,52] and such effects are commonly (and correctly) reported on the drug leaflets: Patients finding out that the same drug they have been prescribed for treatment of PE can impair erection might be doubtful of the prescription's adequacy and might therefore refrain from correct use. It is therefore unsurprising that many patients, when being proposed treatment with off-label SSRIs, are more reluctant to start and more likely to discontinue treatment.[43,67] These side effects are very much less frequent for Dapoxetine than for other SSRIs, but stigmatization of the whole drug class might mislead patients, who may receive wrong explicit or non-explicit wrong messages from the doctor, regarding efficacy and/or possible side effects, resulting in unwillingness to pursue treatment. This possible nocebo effect,[71] better defined as "drucebo" effect[72] could be produced by the prejudices of the doctors based not on evidence, but on opinions, and/or on the ignorance that the safety profile of antidepressant SSRIs is largely because of their pharmacokinetics and to their ability to cross the blood–brain barrier. In these regards, cultural differences might become once again one of the main reasons for different rates of treatment compliance. It is likely that a greater tendency toward self-care might be an additional reason for poor compliance in some countries: A good doctor–patient relationship can improve adherence to treatment,[73] whereas relying too much on information provided by Internet can potentially become harmful.[74] In the field of andrology and sexual medicine, it is quite common for doctors to visit patients who have "self-prescribed" pro-erectile drugs (i.e., PDE5 inhibitors, such as sildenafil, tadalafil, vardenafil, and avanafil), either buying these treatments online or getting them second-hand from friends or colleagues. This behavior carries several risks, from the possible contamination with other pharmacologically active compounds to the delayed diagnosis of any underlying condition affecting sexual function, for example, male hypogonadism or cardiovascular diseases.[75–77] As such, establishing a reliable doctor–patient relationship is necessary to increase compliance to treatment and prevent the progression of subclinical to overt forms of sexual dysfunctions.[12,13] Cultural differences can exist in these regards, and although they have not been adequately investigated so far, it is fairly likely that Eastern and Western cultures might have different approaches to sexual health, and to PE in particular. Additionally, it should be considered that sexual health can be considered a reliable clinical biomarker, or rather a surrogate marker, of systemic health.[78] Sexual medicine is, in fact, a fundamental part of systems medicine,[78] that is, the interdisciplinary field of research that considers the interaction between the human body and genomic, behavioral and environmental factors, and sexual dysfunctions, sharing the same risk factors as most non-communicable diseases, can be considered the proverbial "canary in the gold mine" for subsequent clinical evaluation.[79] To an extent, it can be hypothesized that sexual medicine might play a role in more complex theories focusing on overall health, such as the developmental origin of health and diseases[80–82] or the "one health" approach.[83] China is among the most active countries in PE research[17]: It can be supposed that such dynamic interest in research is an echo chamber for the concerns of the general population, and that therefore request for medical support for management of PE is higher than elsewhere despite similar prevalence.[84] This can possibly be because of the high importance given to female sexuality in East Asia,[7,13,85] or to the perception of PE as a more thorough health concern.[86] In fact, a well-consolidated tradition of positive attitudes toward sexuality is present in the Chinese culture grounded in Taoism, which is "one of the few [indigenous religions in the world] that has stressed the importance of using sexual techniques for individual benefits".[87] For example, the notorious Chinese intellectual Zhang Jingsheng (1888–1970) theorized the "Third Kind of Water" (*disanzhong shui*) theorizing the pursuit of sexual pleasure.[88] Moreover, it is a characteristic of the TCM and of the Chinese doctors in general

to discuss problems with the patients with a closer attention to their needs and expectations than in a typical hasty urological visit in Western countries, usually more concentrated on the symptom (in this case the PE) than on the patient (in this case the couple). Unlike Western medicine, TCM requires a dialectical treatment based on the overall condition of the patient's body. Depending on each person's condition, there may even be cases where the principles of medication are completely opposite. This depends to a large extent on the doctor's judgment of the symptoms, which so far cannot be fully standardized and objectified, and is one of the major reasons why it is difficult to conduct clinical research in TCM. Some symptoms are more frequently associated with particular "phenotypes" (e.g., Yin deficiency, kidney Qi deficiency, damp-heat syndrome) and can be treated by administering different herbal preparations (e.g., Cinnamomi Cortex, Rehmanniae Radix, Common Macrocarpium Fruit, etc.) following careful evaluation by a TCM expert clinician. Formulas are often prepared with different ingredients and can be taken in different shapes, such as teas, pills, and tinctures. Additionally, other non-herbal treatments are available, such as acupuncture and moxibustion, which overall complement the wide spectrum of disease that can be treated by TCM. Finally, another reason for the success of the Chinese approach to PE with respect to that common in the Western countries could be found in the particular eclectic attitude to associate different treatments, even from different cultures.[89] This therapeutical strategy could be particular successful in a multifaceted and complex symptom, such as PE.[90] Clearly, such claims deserve further confirmation in future studies addressing the preferences for PE patients toward different treatments.

This study is, to our best knowledge, one of the largest ones to investigate PE in a real-life sample of patients attending different Centers with a solid knowledge of PE research. However, it also has several limitations. The study was carried out in a single Country (People's Republic of China), and as such whether these results can be generalized to a broader audience is an open question. Clinical data of patients attending these centers were only partially available, and as such addressing the presence of underlying comorbidities was not feasible. The dosage of Dapoxetine (30 or 60 mg) was not thoroughly collected, therefore adding a possible source of bias.

5 | CONCLUSIONS

PE is a complex sexual dysfunction with a multifactorial pathogenesis, which is largely underreported, under-investigated, and undertreated. Several therapies are available, including drug treatments whose efficacy has been disputed in previous research. In this real-life study on a large population of patients attending different Centers in China, 20.9% came for a primary complaint of PE. Patients were treated according to clinicians' practice and judgment: Overall, most patients received treatment with Dapoxetine, either alone or in combination, and this treatment was likewise the most reliable one, according to the fewer requests for treatment switch. Although results cannot be generalized, this study highlights how both efficacy and reliability of Dapoxetine, a Waterloo in the Western, European, and Flemish opinions and a success under the shadow of the Great Wall, is much higher than perceived by Western doctors who may find in the real-life data presented here some reasons to modify their attitudes.

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CONFLICTS OF INTEREST STATEMENT

EAJ is or has been a speaker and/or paid consultant for Bayer, Ibsa, Lundbeck, Menarini, Merk-Serono, Otsuka, Pfizer, Shionogi, and Viatris. AS has been a paid consultant for Menarini. All others declare not to have any conflict of interest for the present manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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