

MINI-REVIEW

Research progress on the treatment of premature ejaculation by integrated traditional Chinese and Western medicine

Peng Xu^{1,†}, Jingkai Wang^{1,†}, Hailuo Wang^{2,†}, Ruoran Zhang¹, Kun Pang^{2,3,4,*}¹School of Medicine Jiangsu University, Jiangsu University, 212001 Zhenjiang, Jiangsu, China²Department of Urology, Xuzhou Central Hospital, Xuzhou Clinical School of Xuzhou Medical University, 221000 Xuzhou, Jiangsu, China³Department of Urology, Peixian People's Hospital, 221000 Xuzhou, Jiangsu, China⁴Nanjing University of Chinese Medicine, 210000 Nanjing, Jiangsu, China***Correspondence**paking@xzhmu.edu.cn
(Kun Pang)

† These authors contributed equally.

Abstract

Premature ejaculation (PE) is a common condition that troubles men in today's society, which significantly influences men's mental health and the relationship between spouses. Both traditional Chinese medicine (TCM) and Western medicine are currently the preferred treatment options for PE. When treating PE with both traditional Chinese and Western medicine, two sets of treatment plans are briefly introduced: internal treatment and external treatment. In the internal treatment method, the popular TCM formulas in recent years were introduced, their therapeutic effects and principles on PE were described, and the results of analyzing the effective ingredients of TCM monomers from the perspective of molecular biology in recent years were also presented. Then the mechanism of their treatment of PE was explained and their efficacy and safety was compared with Western medicine in treating PE; in terms of external treatment, the current mainstream treatment schemes were introduced, such as acupuncture and moxibustion, liquid medicine external application, massage desensitization and behavioral psychotherapy, and their advantages and disadvantages were elaborated. Finally, the theoretical treatment of PE was put into practice through rational criticism and analysis to improve men's physical health and promote the development of the TCM culture.

Keywords

Premature ejaculation; Traditional Chinese medicine; Behavioral therapy; Acupuncture and moxibustion; Reproductive health

Progreso de la investigación en el tratamiento de la eyaculación precoz con la medicina tradicional China y occidental integrada

Resumen

La eyaculación precoz (PE) es una enfermedad común que afecta a los hombres en la sociedad actual y puede tener un impacto significativo en la salud mental y las relaciones conyugales de los hombres. En la actualidad, tanto la Medicina Tradicional China (MTC) como la medicina occidental son los tratamientos preferidos para la PE. En el tratamiento de la medicina tradicional china y occidental integrada, presentamos brevemente dos conjuntos de planes de tratamiento: tratamiento interno y tratamiento externo. En términos de tratamiento interno, hemos introducido las recetas de MTC que han sido populares en los últimos años, sus efectos terapéuticos y principios sobre el PE, y los resultados del análisis de los principios activos individuales de la medicina tradicional china desde la perspectiva de la biología molecular en los últimos años. Explicamos su mecanismo para tratar la PE y la comparamos con la eficacia y seguridad de la medicina occidental para tratar la PE; En términos de tratamiento externo, hemos presentado los programas de tratamiento convencionales actuales. Como la acupuntura y la moxibustión, la aplicación externa de pociones, la desensibilización por masaje y la psicoterapia conductual, y se introdujeron sus ventajas y desventajas. Por último, el tratamiento teórico de la EP se puso en práctica mediante la crítica y el análisis racionales para mejorar la salud física de los hombres y promover el desarrollo de la cultura de la MTC.

Palabras Clave

Eyaculación precoz; Medicina Tradicional China; Terapia conductual; Acupuntura y moxibustión; Salud reproductiva

1. Background

Premature ejaculation (PE) is a common condition that plagues men in modern society [1]. According to different clinical classifications and definitions, approximately 20%–30% of men suffer from varying degrees of PE [2]. Historically, there have been many different definitions of premature ejaculation (PE), but these definitions have no scientific basis and lack diagnostic standards. In 2014, to overcome the limitations of previous definitions, the International Society for Sexual Medicine (ISSM) developed a unified and evidence-based definition of PE [3], as follows: a troublesome shortened ejaculation latency in which ejaculation always or almost always occurs before vaginal penetration or within 0 to 1 minute after vaginal penetration is called congenital PE, acquired PE is defined as ≤ 3 minutes after vaginal insertion [4]. We analyze the causes of PE by breaking down the process of male orgasm, which includes: desire, excitement, orgasm and ejaculation [5]. Patients with pulmonary embolism may have excessive stimulation of the bulbocavernosus reflex guided by the sympathetic nervous system, which stimulates the prostatic urethra and is one of the important pathophysiological factors [6]. However, to reach orgasm, men need exogenous stimulation of the abundant nerves on the head of the penis and nerves in other parts of the body; it also requires the emotional stimulation threshold to reach orgasm. Therefore, we can divide the influencing factors of premature ejaculation into physiological factors and mental factors. Traditional Chinese medicine (TCM) has a long history of treating PE. As early as 168 Before Christ (BC), the *Medical Book of the Han Tomb in Mawangdui* recorded PE. In the *Secret of the Jade Chamber*, it is described that “The man reluctantly engages in sexual intercourse when his penis is not yet erect, coupled with wrong behaviors such as forced ejaculation during sexual intercourse, which leads to the exhaustion of essence and blood; or the man has sexual intercourse after overeating, thus injuring the spleen, causes severe indigestion, atrophy of penis, loss of essence and blood.” This is also an early understanding of PE by ancient Chinese people.

2. Diagnosis of PE

There are many methods to diagnose PE. Currently, the most common ones include questionnaires, psychological assessments and equipment testing. Questionnaires and psychological evaluations can obtain basic elements of medical history, psychological status, and sexual history [7], such as sexual activity (sexual intercourse or masturbation), sexual desire, and sexual intercourse satisfaction [8]. This method can perform operating characteristic curve analysis on the obtained data by integrating computers, and suggest whether the patient needs psychological treatment or organic treatment through a psychological study of the patient, related instruments include the SIEDY scale 3 (Structured Interview for Erectile Dysfunction scale 3) [9]. This instrument can evaluate and analyze the patient’s psychological activities to clarify the diagnosis and guide the treatment process. Currently, common equipment testing instruments include penis bioshock threshold measures. It infers penile sensitivity by measuring the penis bioshock

threshold and determines the penis vibration perception threshold through the bulbocavernosus reflex. Vibration detectors are placed on the head of the penis and both sides of the penis body, and the vibration amplitude is continuously increased. When the patient perceives the stimulation, it is recorded as the threshold. Using bio-vibration wave technology, we can quantitatively evaluate the sensitivity level of sensory nerves in various parts of the penis by measuring the bio-vibration sensory thresholds in various parts of the penis, and assess the conduction function of sex-related nerves and the regulation of sexual excitement by the central nervous system. Vibration sensation threshold testing is the best way to test sensitivity. The vibrometer generates steady and repetitive vibration stimuli to calculate tactile thresholds. Besides, there is a clear correlation between ejaculation latency and penis vibration sensory threshold [10].

3. Syndrome differentiation and treatment of PE

Currently, there are numerous treatment options for PE. We searched existing articles and found that the main options are targeted at the physiological and mental factors that cause PE. Current research on the pathophysiology of PE generally holds that the occurrence of PE is inseparable from dopamine and the neurotransmitter serotonin in the cerebral cortex and synapses [11]. Dopamine, as an important neurotransmitter, also plays an important role in the ejaculation process. Dopamine regulates human activity and ejaculation mainly through the dopamine transporter (DAT) and dopamine receptor (DAR) [12]. The most common representative drug of this type of mechanism is the DAR antagonists. In an experiment [13] on delayed ejaculation in rats induced by the selective dopamine D3 receptor antagonist SB-277011, it was demonstrated that male rats using SB-277011 had delayed ejaculation during sexual intercourse. The ejaculation latency is prolonged, effectively confirming delayed ejaculation. Male rats treated with SB-277011 experienced an increase in ejaculation latency during sexual intercourse, effectively confirming delayed ejaculation. In addition, the relationship between 5-hydroxytryptamine (5-HT), an important neurotransmitter released from the presynaptic, and PE was confirmed as early as the 20th century, and it was divided into serotonin 2C receptor hyposensitivity and serotonin 1A receptor hypersensitivity [14]. Therefore, selective serotonin reuptake inhibitors emerged. The main principle is to selectively bind to the 5-HT uptake transporter, reduce its transport of 5-HT into the synaptic cleft, and thereby increase the concentration of 5-HT in the synaptic cleft, allowing it to combine with 5-HT_{2c} to increase the ejaculation threshold and delay ejaculation (Fig. 1). 5-HT reuptake inhibitors have long been considered the first-line treatment for PE. In addition, in recent years, multiple pieces of evidence have shown that oxytocin also plays an important role in the ejaculation process of vertebrates [15]. A new type of drug currently being studied for treating PE is an oxytocin antagonist. Epelsiban is the first oxytocin antagonist in clinical trials for treating PE [16]. However, due to the limitations of Epelsiban’s efficacy, Murat Gul *et al.* [16] proposed a study on Cligosiban, another oxytocin antagonist.

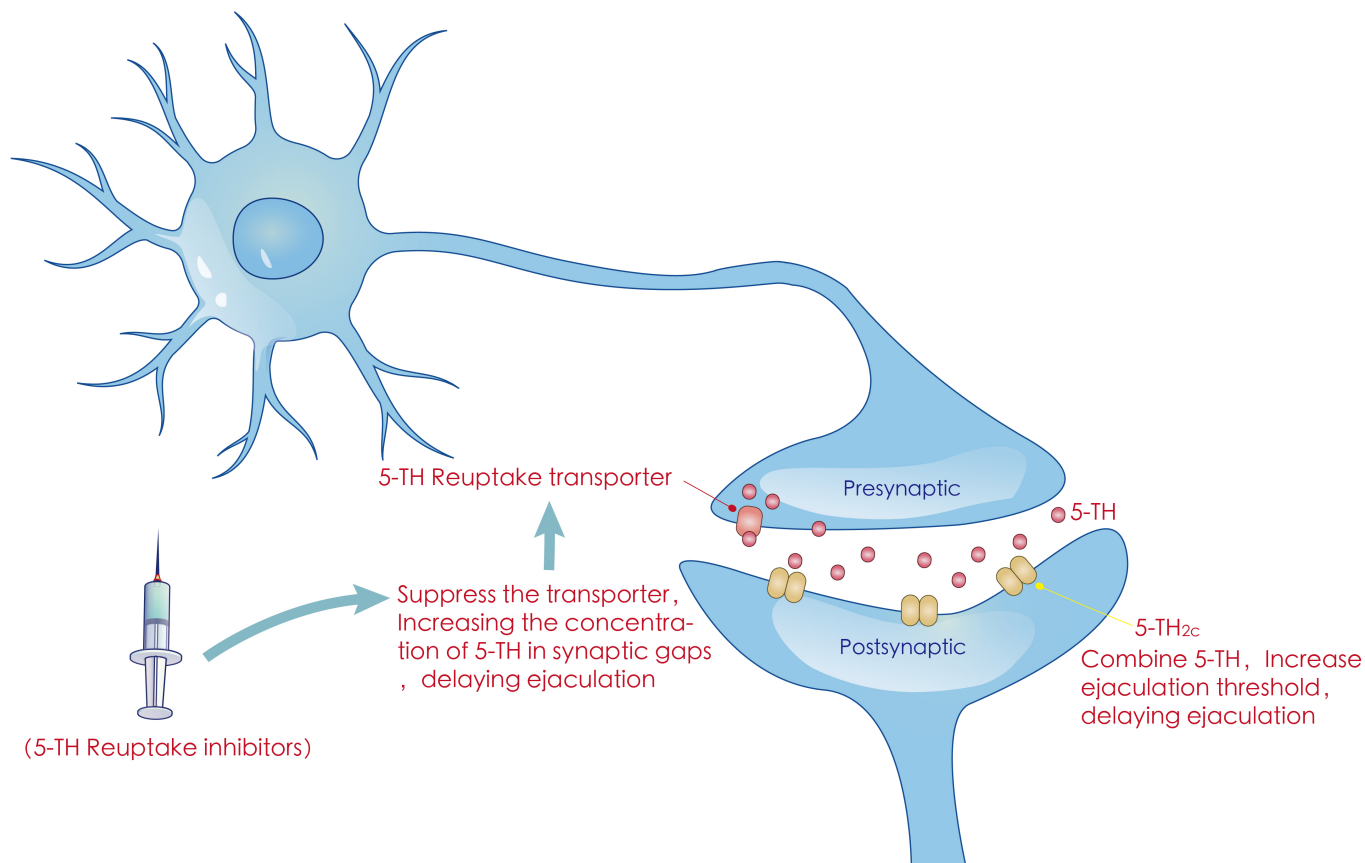


FIGURE 1. The figure shows the use of 5-HT reuptake inhibitors to inhibit transporters and increase the concentration of 5-HT in the synaptic cleft, which increases ejaculation threshold and delays ejaculation. 5-HT: 5-hydroxytryptamine.

In controlled clinical trials, it was shown that the geometric mean vaginal latent ejaculation period value in the Cligosiban group increased by 2.1 times, which was significantly higher than the value in the placebo group (1.1 times, $p = 0.079$). However, there is currently limited research on this drug, and its clinical efficacy is relatively low compared to other drugs. In addition, the understanding of its complications remains unclear. Therefore, there is still a requirement for relevant randomized controlled trial (RCT) literature support and the emergence of iterative drugs. Moreover, SSRIs (Selective Serotonin Reuptake Inhibitors) have many side effects, such as nausea, vomiting and dry mouth. There is also evidence suggesting uncertainty regarding the efficacy of its treatment [17, 18]. In recent years, many studies have indicated that TCM has favorable efficacy in treating PE and has fewer side effects [19]. This article will describe in detail the latest advancements in TCM treatment and the combination of traditional Chinese and Western medicine in treating PE.

3.1 TCM treatment

3.1.1 Shugan Yidan formula

The Shugan Yidan Formula is a TCM prescription that comes from *The Comprehensive Collection of Prescriptions by Famous Contemporary Chinese Doctors*. Its main ingredients include *Bupleurum*, *Citrus aurantium*, *Paeoniae Rubra Radix*, *raw licorice*, *Scutellaria baicalensis*, *Coptis chinensis*, *Rehmannia glutinosa*, *Gallus gallus gallinae*, *Polygala* and

Codonopsis. Related articles have proven its effectiveness in treating PE through animal experiments.

Han *et al.* [20] added the Shugan Yidan Formula to a rat model intervened by the DAR agonist-pibedil and then analyzed it. They found that its main function was regulating the level of DAR through *Bupleurum* and *Polygala* to delay ejaculation [20]. By collecting rat hypothalamic tissue for Real-time Quantitative Polymerase Chain Reaction (RT-qPCR), it was found that the expression of DAT was significantly reduced in the PE model, while low-dose treatment of the Shugan Yidan Formula could significantly increase the expression of DAT. The expression of DA receptors (D2/D3) in the PE model group was higher than that in the control group, and the addition of the Shugan Yidan Formula significantly reduced the mRNA expression of both receptors. In recent years, a clinical study on the effect of the dopamine D3 receptor agonist 7-hydroxy-2-(di-N-propylamino) tetralin on PE also demonstrated the promoting effect of dopamine D3 receptors on ejaculation [21]. This indicates that the dopamine D3 receptor may be an important target for treating PE. However, this study merely focused on changes in dopamine D3 in the hypothalamus. The alterations in dopamine D3 in the brain's other parts are currently unknown. Therefore, the impact of Shugan Yidan Formula on PE and the influence of its specific components are also worthy of further study.

3.1.2 Yimusake tablet

Yimusake tablet (YMSK-T) is a traditional prescription from Eastern Uyghur medicine in China. It mainly consists of 11 TCMs, including *Bletilla striata*, musk, ambergris, saffron, nux-vomica, mastic-frank incense, bullwhip, nutmeg, cloves, poppy shells and galangal. As early as 1998, the Uyghur Drug Standards of the Ministry of Health of the People's Republic of China mentioned that YMSK-T has kidney-yang, nourishing, and astringent effects. YMSK-T has been used to treat diseases such as impotence, PE, enuresis, and renal failure. In a study on the drug YMSK-T, the number of spermatogenic cells in the epididymal seminiferous ducts of rats under the influence of high-dose YMSK-T increased significantly, while the rats under the influence of moderate doses of YMSK-T also experienced varying degrees of increases in various stages. These mainly include primary spermatocytes and secondary spermatocytes [22]. However, this is not enough to prove its improvement effect on PE. An analysis of the ingredients in the drug showed that the *Bletilla striata* contained in YMSK-T had the effect of nourishing the kidneys and enhancing self-control. Galangal can warm kidney yang, improve kidney function, and enhance reproductive capacity. In addition, in another study, rats treated with YMSK-T reversed the expression changes of eight miRNAs associated with the occurrence of impact [23], indicating the effectiveness of the drug in treating male sexual dysfunction. In terms of toxicology research, through the analysis of acute and chronic toxicology studies, YMSK-T exhibits toxicity to rats at a dose of 9.19 ± 1.24 g/kg. Within safe doses, YMSK-T has no side effects on the liver, respiratory, and cardiovascular systems. This also demonstrates that YMSK-T is a safe, effective, and highly promising drug, which also provides a new option for the treatment of PE by tonifying the kidney and strengthening yang. However, research on this drug is currently only confined to animal experiments. The research on the side effects of YMSK-T on the human body is currently unknown. The author hopes there will be more clinical trials of this drug in the future to prove its safety in the human body.

3.1.3 QiaoShao formula

The TCM QiaoShao formula (QS) is a drug used clinically to treat PE. Its main ingredients are Hypericum perforatum, white peony root, *Bupleurum*, *astragalus*, *Morinda officinalis*, *yam* and *calamus*. There was a randomized controlled trial of QS and Dapoxetine which showed that [24], compared with the patients in the control group treated with Dapoxetine, the scores of the patients in the treatment group who received QS were significantly improved on the TCM Symptom Score (CMSS) and Sexual Life Satisfaction (SLS). It demonstrated non-inferiority in the Chinese PE Diagnostic Tool (PEDT) score index. In terms of adverse events (AEs), three patients with dizziness symptoms and two with nausea symptoms occurred in the control group, while no similar symptoms emerged in the treatment group, proving the safety of the drug. In a network pharmacology study on QS, 54 compounds, 61 targets, and 20 pathways were identified in the 7 traditional Chinese medicines of QS [25]. In addition, the study also verified through clinical trials that QS affected serum 5-HT,

nitric oxide (NO), oxytocin and thyroid hormones in PE patients. Through the analysis of the 7 ingredients in QS, it was also found that the active ingredient in *Forsythia suspensa* that affected PE was St. John's wort, which inhibited the uptake of serotonin and dopamine [26]. Ingredients such as *Bupleurum* and White Peony also play a role in regulating serotonin and dopamine [27], all of which play an important role in treating PE.

3.1.4 Combination of traditional Chinese and Western medicine

For the treatment of PE, TCM can frequently be combined with Western medicine. Some reports indicate that the TCM Qilin Pills and sertraline hydrochloride were combined to treat PE [28]. Sertraline hydrochloride is a highly selective SSRI drug that can block the reuptake of 5-HT, leading to an increase in the concentration of 5-HT in the synaptic cleft and improving the symptoms of PE [29]. Qilin Pills are made of a variety of TCM ingredients. Among them, *Epimedium* and *Cuscuta* have the effect of nourishing *Cynomorium* and nourishing the kidneys and aphrodisiac, Mozao lotus, mulberry seeds, wolfberry seeds, and raspberries nourish yin and nourish the kidneys to achieve the effect of nourishing both yin and yang and seeking yang from yin. They are used to treat impotence, premature ejaculation, and oligospermia caused by deficiency of kidney essence and insufficient qi and blood. In this paper, a comparative study was conducted on the Qilin Pill group alone, the Sertraline Hydrochloride group alone, and the combined Qilin Pill and Sertraline Hydrochloride group, respectively. It was found that the combined use of Qilin Pill and Sertraline Hydrochloride group was significantly better than the other two groups [28]. Coincidentally, in a study on the safety and effectiveness of QS prescription combined with dapoxetine, the ejaculation latency of patients treated with QS combined with dapoxetine was also significantly longer than that of patients treated with dapoxetine alone [30]. According to current research, combined traditional Chinese and Western medicine treatment has better efficacy than medication alone. However, so far, fewer drug combinations have been studied, and the sample size of current studies on drug side effects is also small. To reduce the side effects of SSRIs and anti-dopamine drugs such as nausea, vomiting, and dry mouth, it is appropriate to reduce the dosage of the drugs, adjust the proportion of Chinese and Western medicines, and explore the optimal doses of Chinese and Western medicines. This may be a meaningful research direction for studying the combination of TCM and Western medicine in treating PE.

3.2 External therapy

For the treatment of PE, in addition to taking medication, the commonly used methods in clinical practice include external drug therapy. According to the latest PE treatment guidelines released by ISSM, psychotherapy/behavioral therapy or drug treatment can be regarded as first-line treatment options for primary PE [31]. The use of drugs such as dapoxetine or SSRI is the first-line treatment option for primary PE. Topical medication can be used as an alternative. Compared with systemic drug therapy, topical drug therapy is more intuitive

and easier to operate. According to the recent ISSM guidelines, topical drug therapy also has fewer adverse drug reactions and side effects than systemic therapy with internal drugs [32].

3.2.1 lidocaine-prilocaine spray

Lidocaine-prilocaine spray is a topical drug for the treatment of PE. This medication consists of an aerosol of lidocaine and procaine dissolved in a non-chlorofluorocarbon propellant, and the formula also acts as a solvent, thus forming a eutectic-like mixture [33]. Unlike other topical drugs, this drug has a high selectivity for the glans penis. Due to the molecular weight of its unique water formula, it can easily penetrate into the glans penis, but cannot penetrate into the skin of the penis' other parts. This design can produce a local desensitization effect on the glans penis [34]. A scholar carried out a double-blind controlled study on the improvement of ejaculatory latency, control and sexual satisfaction with lidocaine and prilocaine spray, and in this study, the patients were divided into a lidocaine-prilocaine spray treatment group and a placebo control group. The efficacy of the two groups was compared through indicators such as the PE index (IPE) and intravaginal ejaculatory latency time (IELT) [35]. The final results found that applying lidocaine-prilocaine spray topically to the glans penis 5 minutes before sexual intercourse could significantly improve ejaculation latency, ejaculation control, sexual satisfaction, and sexual pain, and both patients and partners showed good tolerance.

3.2.2 TCM spray combined with desensitization therapy

In a clinical randomized controlled trial of TCM spray combined with desensitization therapy, Cui *et al.* [36] used an alcohol soaking method to prepare TCM spray from asarum, cyperus rotundus, mantis, aconite, schisandra chinensis, rose hip, madder fruit, and Zanthoxylum bungeanum peel. The patients were divided into a pure TCM spray group, a TCM combined with a desensitization therapy group and a pure desensitization therapy group. By comparing the IELT and the Chinese Index of Premature Ejaculation Sexual Function (CIPE-5) to observe the efficacy of the three treatment options, the study found that the IELT (2.99) of the pure TCM spray treatment group was significantly improved compared with the pre-treatment (1.15). In terms of CIPE-5, there was also a significant improvement after treatment (19.69) compared with before treatment (9.93). By comparing the differences between the groups, the efficacy of the TCM spray combined with a desensitization therapy group (89.7%) was also much higher than that of the TCM treatment group (65.5%) alone, thus proving the effectiveness of the combination therapy. However, this study only compared the clinical efficacy of drugs. Due to the diversity and complexity of TCM ingredients, analyzing the specific ingredients of TCM and the mechanism of related ingredients in treating PE can also be based on the analyzed effective ingredients. Therefore, the composition and dosage of TCM should be optimized and need to be further studied.

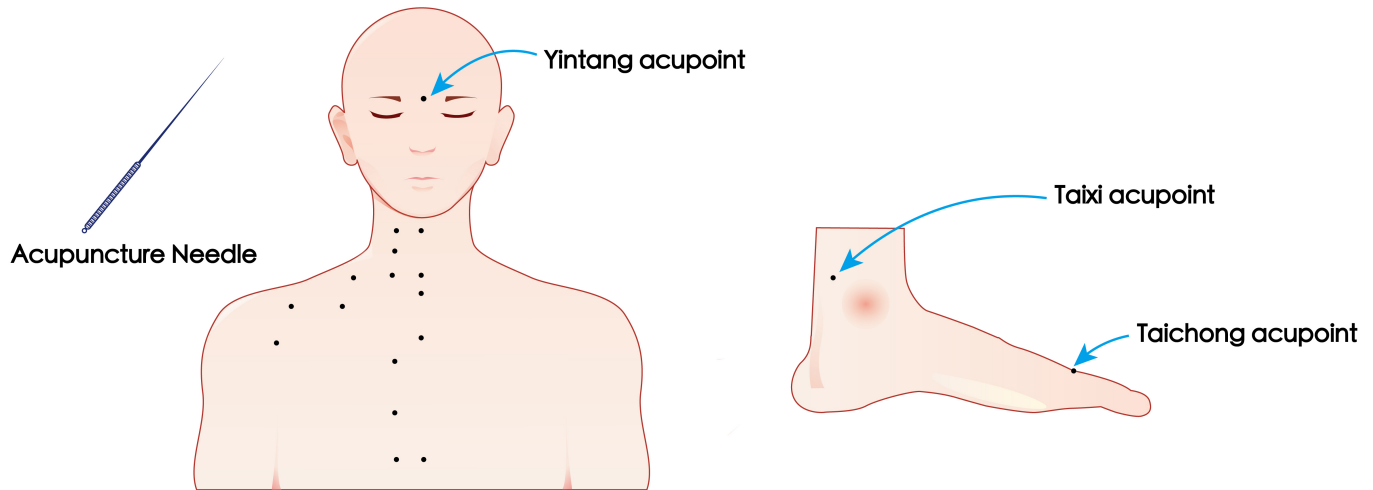
3.2.3 Hydromedicine massage desensitization therapy

This method mainly uses the principle of arterial blood flow to activate the blood circulation of the organ and promote rapid congestion of the corpus cavernosum, thereby improving the fibrous tissue at the root of the penis and increasing the thickness of the corpus cavernosum albuginea. The hydromedicine massage method aims to dissolve yohimbine and other tablets in warm water, and it is introduced into body tissues in the form of ions to achieve therapeutic purposes, such as stimulating the penis and reducing the sensitivity of the glans penis through repeated massage [37], prolonging ejaculation time, and increasing the ejaculation sensitivity threshold. By alternating vacuum attraction, blood is stirred in the penile arteries and corpus cavernosum to increase capillary permeability, enhance cell tolerance, activate dormant cells, and repair damaged and occluded blood vessels [38].

3.2.4 Acupuncture therapy

Acupuncture therapy, as one of the most commonly used, most distinctive, most effective, and most representative therapies in TCM, has a history of more than 3000 years in China [39]. According to current research, the principles of acupuncture are mainly divided into two categories: local stimulation releases vasoactive substances and improves local blood supply. Pain stimulates the driving center and the descending pathway to achieve systemic regulation [40]. In recent years, research on acupuncture treating PE has gradually made good some achievements. Studies have found that acupuncture and moxibustion could regulate the release of serotonin and testosterone levels through pain stimulating the central regulatory pathway, and on this basis, regulate ejaculatory reflex [41]. Sahin *et al.* [42] found that both acupuncture and moxibustion and acupuncture and moxibustion therapy had achieved effective therapeutic effects through a comparative study on the treatment of PE with dapoxetine, and the score of vaginal ejaculation latency and PE diagnostic tool in dapoxetine group was significantly better than that in the acupuncture and moxibustion treatment group. However, three patients in the dapoxetine group withdrew from the study due to nausea due to adverse reactions, and no related adverse reactions occurred in the acupuncture and moxibustion group.

There is a randomized clinical controlled trial of acupuncture and Paroxetine in the treatment of PE [43], and the patients were divided into an acupuncture treatment group and a paroxetine treatment group. In the acupuncture treatment group, Zusanli, Hegu, Taixi, Taichong, Yintang, Zhongji and De Qi points were selected according to *the World Health Organization Western Pacific Region Standard Acupoint Locations*, and acupuncture was performed on both sides and left for 20 minutes (Fig. 2). Studies have found that acupuncture treatment has a stronger effect on delaying ejaculation than placebo treatment. Compared with placebo treatment, TCM acupuncture treatment is characterized by lower side effects and better efficacy, so it deserves further research as an alternative to PE treatment.



Acupoint distribution map

FIGURE 2. The figure shows the distribution of acupoints such as Taixi, Taichong and Yintang.

3.3 Psychological/behavioral therapy

Depending on the cause of PE, psychological/behavioral therapy also plays an important role as an auxiliary treatment for drugs and as an alternative treatment for patients who cannot tolerate drugs in treatment plans targeting mental factors. Studies have shown that the occurrence of PE is inextricably linked to the stress experienced by humans. Fiala *et al.* [2] used diagnostic tools to score traumatic stress and body dissociation in patients with PE and used cortisol measurement to study the correlation between PE and stress. They found a link between secondary premature ejaculation and traumatic stress scores, as well as cortisol levels in the patients' blood. In another study, 207 PE patients were screened based on the text revision standards of the Diagnostic and Statistical Manual of Mental Disorders (DSMMD, 4th Edition). PE patients and their partners generally report lower satisfaction with sexual function, lower overall quality of life, and heavier psychological burden [44]. Bukhari *et al.* [44] studied the findings of psychotherapy in PE that the combination of medication and psychotherapy are more effective than medication alone. It has a significant effect on improving men's sexual skills. Psychological and behavioral cognition of sexual dysfunction has also been improved. In terms of behaviors, some studies conducted controlled trials on PE patients through yoga therapy. Through analysis, it was found that yoga exercises through various postures, mudras, bandhas and pranayama [45], as well as lower abdominal massage plus steam bath, hip bath plus yoga, and lower abdominal mud natural therapies such as compressing and acupressure can improve the symptoms of PE to varying degrees [46]. In addition, studies have found that high-intensity interval training has a favorable effect on the treatment of PE [47]. In terms of behavioral therapies such as yoga and exercise, through contraction training of pelvic floor muscles, the contraction force of pelvic floor muscles and the ability to control ejaculation can be enhanced, and the self-confidence in sexual behavior can be boosted to achieve a positive promotion effect on the treatment of PE. Some

studies also improve PE by employing an electrical stimulation device for transcutaneous stimulation of the perineum. These methods can enhance pelvic floor muscle contractility through human intervention [48]. Psychological/behavioral therapy, as an alternative therapy to drugs, can avoid the side effects of drugs on the human body to a certain extent and has excellent development prospects and research value.

4. Prospect

PE is a common condition that plagues men in today's society. Its impact on both couples is self-evident. The current mainstream treatments for PE are 5-TH reuptake inhibitors and DAR antagonists. These drugs have been used clinically for many years and have achieved good efficacy and have been widely promoted, but the accompanying side effects and patient tolerance issues cannot be ignored. Therefore, TCM and combined traditional Chinese and Western medicine have good research and clinical application prospects as alternative therapies. Based on some clinically controlled studies and pharmacological studies of some TCM prescriptions in the treatment of PE in recent years, this article found that TCM prescriptions are effective in treating PE and have good complications. Studies on the mechanism of TCM in treating PE have found that the TCM monomers contained in TCM prescriptions can delay ejaculation through multiple DAR and 5-TH pathways. However, more research is still needed to support the specific action pathways and targets of TCM monomers. As an effective treatment for PE, TCM can effectively reduce the dosage of Western medicine in the treatment of combined traditional Chinese and Western medicine, thereby reducing the related side effects of Western medicine. For various TCM prescriptions and monomers and combined treatment with Western medicine, there are few drug compatibility schemes, and it is worthwhile to further discover more treatment options to improve patients' symptoms and reduce side effects. In terms of external treatment methods, massage, desensitization, pharmaceutical spray and other programs have made good progress

in research in recent years. As an important way for traditional medicine to treat PE, acupuncture has many advantages such as a good curative effect, a quick effect, and few side effects. It utilizes the pain of local acupuncture to stimulate the release of vasoactive substances and improve local blood supply. The stimulation of pain will also prompt the central nervous system to regulate the whole body. Currently, there are many acupuncture point programs. There are currently few studies on the specific mechanism of nerve-humoral regulation in the treatment of PE. Acupuncture is an important alternative in the treatment of PE. The therapy's treatment mechanisms and different acupoint selection programs for different groups also deserve more in-depth study. By using the holistic view of TCM, we can combine TCM treatment, acupuncture, behavioral and psychological therapies, start from both the physical and psychological aspects of the patient, and achieve a multifaceted treatment based on the specific conditions of different patients and through internal and external treatments. The combination of treatment methods can improve the patient's PE condition and improve the patient's quality of life from the overall perspective of TCM.

AVAILABILITY OF DATA AND MATERIALS

All materials are available and relevant permissions have been given.

AUTHOR CONTRIBUTIONS

PX and KP—envisaged this review paper; wrote the manuscript. JKW, HLW and RRZ—provided help and advice on bibliography retrieval. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This is a review paper and did not need ethical clearance.

ACKNOWLEDGMENT

We are grateful to the researchers who conducted the studies included in this report and who made data available to us.

FUNDING

This work was funded by China Postdoctoral Science Foundation (2022M722674); Xuzhou Medical Reserve Talents Project (XWRCHT20220009); Peixian Science and Technology Plan Project (P202410).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Niu C, Ventus D, Jern P, Santtila P. Premature ejaculation among Chinese urban men: prevalence and correlates. *Sexual Medicine*. 2023; 11: qfac015.
- [2] Sajdlova R, Fiala L. Premature ejaculation and stress. *European Psychiatry*. 2022; 65: S282.
- [3] Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, *et al.* An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second international society for sexual medicine *ad hoc* committee for the definition of premature ejaculation. *The Journal of Sexual Medicine*. 2014; 11: 1423–1441.
- [4] Althof SE, McMahon CG, Rowland DL. Advances and missteps in diagnosing premature ejaculation: analysis and future directions. *The Journal of Sexual Medicine*. 2022; 19: 64–73.
- [5] Horvath Z, Hevesi K, Kövi Z, Rowland DL. Identifying an optimal ejaculation latency for the diagnosis of men reporting orgasmic/ejaculation difficulty. *The Journal of Sexual Medicine*. 2023; 20: 821–832.
- [6] Niu C, Santtila P. Effects of physical exercise interventions on ejaculation control. *Sexual Medicine Reviews*. 2023; 12: 106–113.
- [7] Nguyen HB, Nguyen CT, Pham MQ, Hoang L, Sansone A, Jannini EA. Perceived intravaginal ejaculation latency time: the diagnosis of premature ejaculation among Vietnamese men. *Andrology*. 2024; 12: 618–623.
- [8] Xi Y, Zhang H, Colonnello E, Limoncin E, Jannini EA, Zhang Y. The masturbatory premature ejaculation diagnostic tool (MPEDT): a novel psychometric tool to evaluate premature ejaculation during masturbation. *Andrology*. 2022; 10: 333–339.
- [9] Perelman MA. The Sexual Tipping Point®: a mind/body model for sexual medicine. *The Journal of Sexual Medicine*. 2009; 6: 629–632.
- [10] Wu HT, Lee CH, Chen CJ, Sun CK. Penile arterial waveform analyzer for assessing penile vascular function in young adults. *Annals of Biomedical Engineering*. 2011; 39: 2857–2868.
- [11] Gao P, Liu X, Zhu T, Gao R, Gao J, Zhang Y, *et al.* Vital function of DRD4 in dapoxetine medicated premature ejaculation treatment. *Andrology*. 2023; 11: 1175–1187.
- [12] Liu X, Zhu T, Gao P, Gao J, Gao R, Jiang H, *et al.* The role of tyrosine hydroxylase within dapoxetine-assisted therapy against premature ejaculation. *Molecular Biology Reports*. 2023; 50: 3515–3523.
- [13] Clément P, Pozzato C, Heidbreder C, Alexandre L, Giuliano F, Melotto S. Delay of ejaculation induced by SB-277011, a selective dopamine D3 receptor antagonist, in the rat. *The Journal of Sexual Medicine*. 2009; 6: 980–988.
- [14] Waldinger MD, Berendsen HHG, Blok BFM, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behavioural Brain Research*. 1998; 92: 111–118.
- [15] Arletti R, Bazzani C, Castelli M, Bertolini A. Oxytocin improves male copulatory performance in rats. *Hormones and Behavior*. 1985; 19: 14–20.
- [16] Gul M, Bocu K, Serefoglu EC. Current and emerging treatment options for premature ejaculation. *Nature Reviews Urology*. 2022; 19: 659–680.
- [17] Gamidov SIG, Popova AYP, Shatylo TV, Li KIL, Safiullin RIS. Evaluation of the efficacy of dapoxetine in primary and secondary forms of premature ejaculation. *Urologiia*. 2022; 46–49. (In Russian)
- [18] Virtanen S, Lagerberg T, Khemiri L, Suvisaari J, Larsson H, Lichtenstein P, *et al.* Association of selective serotonin re-uptake inhibitor (SSRI) treatment with acute substance misuse outcomes. *Addiction*. 2022; 117: 234–242.
- [19] Sansone A, Yuan J, Hou G, Zhang L, Gao M, Zhang Z, *et al.* 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. *Andrology*. 2024; 12: 247–258.
- [20] Han Q, Guo J, Wang R, Li J, Wang F, Gao Q, *et al.* Mechanism of Shugan Yidan fan, a Chinese herbal formula, in rat model of premature ejaculation. *Basic and Clinical Andrology*. 2023; 33: 25.
- [21] Cinar O, Durmus N, Aslan G, Demir O, Evcim AS, Gidener S, *et al.* Effects of the dopamine D3 receptor agonist 7-hydroxy-2-(di-N-propylamino) tetralin in hyperthyroidism-induced premature ejaculation rat model. To be published in *Andrologia*. 2018. [Preprint].
- [22] Zhai X, Pang K, Li H, Yao X, Wang Z, Tang P, *et al.* Study on

- evaluation of toxicology and quality control of Yimusake tablet. *Journal of Ethnopharmacology*. 2020; 263: 111443.
- [23] Jiang P, Aimaier M, Maimaitiyiming M, Liu F, Ma W, Sataer M, *et al*. Changes of microRNA profile after Yimusake treatment in ED rat model. *Acta Biochimica et Biophysica Sinica*. 2019; 51: 873–875.
- [24] Guo J, Gao QH, Wang F, Yu GJ, Zhang JW, Zeng Y, *et al*. Efficacy and safety of Qiaoshao Formula on patients with lifelong premature ejaculation of Gan (Liver) depression and Shen (Kidney) deficiency syndrome: a randomized controlled trial. *Chinese journal of integrative medicine*. 2016; 22: 889–893.
- [25] Wang M, Wang Q, Du Y, Zhang X. Network pharmacology-based strategy to investigate pharmacological mechanisms of Qiaoshao Formula for treatment of premature ejaculation. *Evidence-Based Complementary and Alternative Medicine*. 2020; 2020: 1418634.
- [26] Uckert S, Bazrafshan S, Sonnenberg JE, Kuczyk MA. Effects of phosphodiesterase inhibitors on the contractile responses of isolated human seminal vesicle tissue to adrenergic stimulation. *The Journal of Sexual Medicine*. 2009; 6: 408–414.
- [27] Lu J, Wang Z, Li S, Xin Q, Yuan M, Li H, *et al*. Quercetin inhibits the migration and invasion of HCCLM3 cells by suppressing the expression of p-Akt1, matrix metalloproteinase (MMP) MMP-2, and MMP-9. *Medical Science Monitor*. 2018; 24: 2583–2589.
- [28] Li JX, Lu QG. Efficacy of Qilin Pills combined with sertraline in the treatment of secondary non-consolidated kidney qi premature ejaculation. *National Journal of Andrology*. 2015; 21: 443–446. (In Chinese)
- [29] Yi ZM, Chen SD, Tang QY, Tang HL, Zhai SD. Efficacy and safety of sertraline for the treatment of premature ejaculation: systematic review and meta-analysis. *Medicine*. 2019; 98: e15989.
- [30] Guo J, Wang F, Zhou Q, Geng Q, Gao Q, Zhang R, *et al*. Safety and efficacy of traditional Chinese medicine, Qiaoshao formula, combined with dapoxetine in the treatment of premature ejaculation: an open-label, real-life, retrospective multicentre study in Chinese men. *Andrologia*. 2021; 53: e13915.
- [31] Niu C, Santtila P. Effects of physical exercise interventions on ejaculation control. *Sexual Medicine Reviews*. 2023; 12: 106–113.
- [32] Cai T, Gallelli L, Verze P, Salonia A, Palmieri A. Prilocaine/lidocaine spray for the treatment of premature ejaculation: a dose- and time-finding study for clinical practice use. *International Journal of Impotence Research*. 2023; 35: 378–384.
- [33] Boeri L, Pozzi E, Fallara G, Montorsi F, Salonia A. Real-life use of the eutectic mixture lidocaine/prilocaine spray in men with premature ejaculation. *International Journal of Impotence Research*. 2022; 34: 289–294.
- [34] Shariev A, Savdie R, Hart K. The effects of steady Freddy, a lidocaine-based pump spray for the treatment of premature ejaculation (PE). *American Journal of Men's Health*. 2022; 16: 15579883221145245.
- [35] Carson C, Wyllie M. Improved ejaculatory latency, control and sexual satisfaction when PSD502 is applied topically in men with premature ejaculation: results of a phase III, double-blind, placebo-controlled study. *The Journal of Sexual Medicine*. 2010; 7: 3179–3189.
- [36] Cui YD, Hu SB, Wu B, Li SJ, Xiang K, Liao ZL, *et al*. Efficacy of combined traditional Chinese medicine spray with premature ejaculation desensitization therapy for the treatment of primary premature ejaculation. *African Health Sciences*. 2017; 17: 603–613.
- [37] Zheng L, Wei LT, Tang QZ, Song CL, Liu WR, Wang KN, *et al*. The sensitivity difference between the glans penis and penile shaft in primary premature ejaculation. *Asian Journal of Andrology*. 2023; 25: 487–491.
- [38] Philip F, Shishehbor MH. Current state of endovascular treatment for vasculogenic erectile dysfunction. *Current Cardiology Reports*. 2013; 15: 360.
- [39] Zhang H, Colonnello E, Sansone A, Wang F, Guo J, Wang C, *et al*. Acupuncture for premature ejaculation: a systematic review and meta-analysis. *Sexual Medicine*. 2023; 11: qfad034.
- [40] Colonnello E, Sansone A, Jannini EA. Acupuncture for male sexual dysfunction in the light of the new sexual traditional Chinese medicine. *The Journal of Sexual Medicine*. 2023; 20: 1228–1229.
- [41] Lu X, Han H, Zhang Z, Chen H, Huang X, Zhang R. Study on the efficacy of electric acupuncture in the treatment of premature ejaculation based on testosterone level. *Journal of Healthcare Engineering*. 2022; 2022: 8331688.
- [42] Sahin S, Bicer M, Yenice MG, Seker KG, Yavuzsan AH, Tugcu V. A prospective randomized controlled study to compare acupuncture and Dapoxetine for the treatment of premature ejaculation. *Urologia Internationalis*. 2016; 97: 104–111.
- [43] Sunay D, Sunay M, Aydoğmuş Y, Bağbancı S, Arslan H, Karabulut A, *et al*. Acupuncture versus paroxetine for the treatment of premature ejaculation: a randomized, placebo-controlled clinical trial. *European Urology*. 2011; 59: 765–771.
- [44] Bukhari SR. Psycho, pharmaco and sex therapy for the treatment of premature ejaculation. *Pakistan Journal of Medical Sciences*. 2022; 38: 2350–2355.
- [45] Niu C, Wen G, Ventus D, Jern P, Nyman TJ, Li Y, *et al*. High-intensity interval training (HIIT) and slow breathing interventions alleviate premature ejaculation (PE) symptoms. *International Journal of Clinical and Health Psychology*. 2024; 24: 100457.
- [46] Mamidi P, Gupta K. Efficacy of certain yogic and naturopathic procedures in premature ejaculation: a pilot study. *International Journal of Yoga*. 2013; 6: 118–122.
- [47] Niu C, Wen G, Ventus D, Zhang Y, Jern P, Santtila P. A 2-week high-intensity interval training intervention improves ejaculation control among men with premature ejaculation. *Andrology*. 2024; 12: 164–178.
- [48] Shechter A, Mondaini N, Serefoglu EC, Gollan T, Deutsch F, *et al*. A novel on-demand therapy for lifelong premature ejaculation using a miniature transperineal electrical stimulator-the vPatch: an as-treated analysis. *The Journal of Sexual Medicine*. 2023; 20: 22–29.

How to cite this article: Peng Xu, Jingkai Wang, Hailuo Wang, Ruoran Zhang, Kun Pang. Research progress on the treatment of premature ejaculation by integrated traditional Chinese and Western medicine. *Revista Internacional de Andrología*. 2024; 22(3): 24-31. doi: 10.22514/j.androl.2024.019.