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Advances in Diagnosis and Treatment of Sexual Dysfunctions in Men: A Comprehensive Review of Late-onset Hypogonadism, Erectile Dysfunction, and Premature Ejaculation

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Abstract: This study aims to describe prevalent male sexual dysfunctions, including late-onset hypogonadism (LOH), erectile dysfunction (ED), and premature ejaculation (PE). We summarize diagnostic evaluation, and current pharmacological approaches, along with international recommendations for managing these disorders. Accurate evaluation using standardized tests with defined thresholds is crucial before initiating treatment for male sexual dysfunction. This review provides a comprehensive overview of standard diagnostic evaluation and treatment of male sexual dysfunctions, with a focus on pharmacological interventions, aiming to a balance between efficacy and safety. While existing literature offers valuable insights, our review underscores the need for precise evaluation before prescribing these medical agents to identify real indications of the treatment. Clinicians should consider individual patient characteristics, potential adverse effects, and evidence-based recommendations when selecting the most appropriate treatment.

Keywords: Sexual dysfunction, Late-onset hypogonadism (LOH), erectile dysfunction (ED), premature ejaculation (PE)

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1. Introduction

Sexual dysfunction is a very common issue in both women and men (1-5). Epidemiological studies have reported that 40% of women and 36.5% of men suffer from at least one sexual dysfunction (6). The rate of sexual dysfunction in American men is 52% (7). Late-onset hypogonadism (LOH), erectile dysfunction (ED), and premature ejaculation (PE) are considered the most frequent sexual disorders in men (8-10). A large population-based study on men aged 40-79 years has estimated the LOH prevalence to be 7.8% (10). A recent study on Iranian men has shown that 35.6% of men complained about their sexual function; ED and PE were the most prevalent problems in this population (8). The prevalence of sexual dysfunction varies based on different factors, especially aging, type 2 diabetes mellitus (T2DM), infertility, and psychological disorders (11-13). According to a systematic review of 76 articles, the ED prevalence varied between 14.3-70% for men aged ≥60 years (9). Moreover, the percentage of ED in men with T2DM and infertility has been estimated at 62.2% to 68.7%, respectively (11, 12). A meta-analysis of 49 publications showed that the risk of ED in men with depression was 1.39-fold more than in those without such a history (13).

Existing research has significantly contributed to our understanding of male sexual dysfunction. However, substantial uncertainties persist in this field. These uncertainties primarily revolve around diagnostic criteria, standardized definitions, and thresholds for sexual dysfunction in men across various research studies (14-18). Furthermore, identifying the most effective pharmacological approaches with minimal adverse effects for managing these disorders remains

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an ongoing challenge (16-20). These uncertainties are often exacerbated by the relatively low level of evidence available from existing studies which suffer from limitations such as small sample sizes of the studies and heterogeneities in methods of hormonal assays, study design, and type and dose of treatments (13, 21-31).

Our research endeavors to address these gaps by summarizing existing evidence and proposing avenues for further investigation. By critically evaluating the available literature, we aim to establish clearer diagnostic criteria, refine standardized definitions, and identify evidence-based treatment strategies with the best efficacy and least adverse effects.

2. Methods

2.1. Late-onset hypogonadism

LOH is a clinical syndrome characterized by reduced testicular function. It results from decreased production and/or action of androgens, as well as impaired sperm production (32). LOH arises due to inadequate stimulation of the testes by the hypothalamic-pituitary-gonadal (HPG) axis, along with congenital or acquired factors that lead to androgen function impairment (33). This prevalent male disorder is characterized by a set of symptoms and signs, including sexual dysfunction, low motivation/ vitality, poor concentration/ memory, hot flashes/ sweating, infertility, body hair loss, gynecomastia, reduced testicular volume, obesity, and reduced muscle mass, anemia, and reduced bone density (34, 35). Accurate assessment of LOH using a reliable assay, followed by TRT, can lead to improvements in the function of various body organs, including sexual function (34).

2.1.1. Screening and diagnostic evaluation of late-onset hypogonadism

Before initiating TRT for men with LOH, it is crucial to identify patients through an appropriate hormonal evaluation method. According to the guidelines from the European Association of Urology, serum concentrations of total testosterone, which has been considered an important part of the evaluation, should be assessed in the morning (between 7 am and 11 am) from fasting serum samples, using a standard assay method.

Hormonal assessments should be repeated on at least two separate occasions. A total testosterone (TT) of 12 nmol/L (3.5 ng/ml) serves as the recommended cut-off point for diagnosing men with LOH. Another important hormonal marker for screening LOH is free testosterone. A threshold of < 225 pmol/l (64.9 pg/ml or 64.9 ng/l) has been recommended to diagnose LOH (36). Measuring follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations is valuable in the differential diagnosis between primary and secondary hypogonadism. In primary hypogonadism, gonadotropin levels are elevated, whereas in secondary hypogonadism, these values are low or inappropriately normal (20, 36). TT and LH measurements should be considered in all men with clinical manifestations of hypogonadism. Serum LH levels ≥ 9.4 IU/L and low total or calculated free testosterone suggest primary hypogonadism. FSH measurement can aid in distinguishing between primary and secondary hypogonadism when LH concentrations are less than 9.4 IU/L. Measuring serum concentrations of prolactin can be beneficial in men with low sexual desire and suggestive signs and symptoms of hyperprolactinemia and low or low-to-normal testosterone. Imagination techniques, i.e., MRI, are essential for those men with abnormal serum levels of prolactin or suspicion of pituitary mass and/or presence of other deficiencies of anterior pituitary hormone or severe hypogonadism (TT< 6 nmol/l). Given that concurrent diseases, drugs, and substances may have adverse effects on testosterone production and action, a thorough medical history can help to identify the etiology of this disease (35, 36).

2.1.2. Testosterone replacement therapy for late-onset hypogonadism: Efficacy, risks, and treatment approaches

LOH is characterized by reduced production and/or action of androgens as well as impaired sperm production (37). Consequently, TRT has emerged as a logical and effective treatment for these patients. Specifically, patients with symptomatic hypogonadism without specific contraindications or significant comorbidities, are appropriate candidates for TRT (35, 36). TRT has gained approval as an effective therapeutic approach with beneficial effects on various organs of the body. TRT is associated with increased sex drive, improved mood, and enhanced memory. TRT can enhance muscle growth and strength while reducing fat mass, leading to improved body composition and decreased obesity risk. Testosterone plays a crucial role in red blood cell production; therefore, TRT in hypogonadal men may be linked to increased HCT levels. Testosterone also influences sex organs, resulting in improved sperm production, erectile function, and prostate growth (38). Several studies have evaluated the efficacy and safety of TRT in hypogonadal men (22-24, 38-42). A meta-analysis of 27 randomized controlled trials (RCTs) involving 1890 hypogonadal men demonstrated a positive effect of TRT on depressive symptoms (25). Likewise, another meta-analysis of 87 RCTs and 51 non-randomized studies (NRS) indicated that testosterone therapy could enhance quality of life, libido, depression, and erectile function in men with sexual dysfunctions. However, it is essential to consider the limitations of this meta-analysis, including potential bias and short treatment durations in the included studies (43). Kumar et al, reported that TRT in hypogonadal patients with T2DM was significantly associated with improvements in their metabolic profiles. Specifically, TRT demonstrated the ability to regulate glucose and hormone levels and improve lipid profiles in these patients (22). A

comprehensive literature review concluded that both transdermal and injectable preparations of testosterone are effective treatments for LOH, particularly when fertility is not a concern. These preparations were linked to significant improvements in sexual function and muscle mass, especially when using transdermal and injectable formulations (40). Furthermore, in older men with low testosterone levels and no well-established medical conditions, testosterone therapy may improve sexual functioning and overall quality of life (38). Despite documenting several beneficial effects of TRT in hypogonadal men with sexual dysfunction, concerns persist regarding the adverse effects of these pharmacological agents. Notably, there is an increased risk of VTE, CVD (cardiovascular disease), and recurrent prostate cancer in men treated with these hormonal agents (23, 41, 42, 44). Regarding VTE, a meta-analysis of 6 RCTs and 5 observational studies including 1,249,640 men found no significant association between TRT and VTE (23). However, due to limited data from RCTs and significant heterogeneities in observational studies, these findings are inconclusive, necessitating further research to evaluate the impact of testosterone therapy on VTE. Additionally, a systematic review of 45 trials involving 5,328 subjects revealed an increased risk of cardiovascular (CV) events in users of TRT aged ≥ 65 years, particularly during the first year of treatment. Interestingly, the type of testosterone administration appears to influence this risk, with intramuscular testosterone associated with a lower CV risk compared to other forms of administration (41). A meta-analysis of 10 studies with 179,631 hypogonadal participants revealed that men receiving testosterone had a lower mortality rate from all causes, compared to the control group. However, TRT was associated with an unfavorable effect on cardiovascular events (42). Concerns persist regarding an increased risk of prostate cancer in TRT users. A double-blinded, placebo-controlled trial on 790 hypogonadal men ≥ 65 years revealed that 12 months of testosterone therapy led to a small, but significant increase in mean serum concentrations of PSA (44). Despite these concerns, more well-designed RCTs with large sample sizes in hypogonadal men treated with TRT are needed to accurately assess the risk of prostate cancer in hypogonadal men treated with TRT. A systematic review of 44 studies indicated that testosterone therapy for hypogonadism was not associated with neither an increased risk of prostate cancer or a consistent effect on prostate-specific antigen levels (21). A network meta-analysis, which included 30 RCTs and 5 cohort studies involving 7,740 men, similarly found that TRT was not related to abnormal PSA changes or an increased risk of prostate cancer in patients with hypogonadism. Intramuscular injection was identified as the best administration type associated with the lowest risk of prostate cancer (24).

Before treatment, all patients should undergo a thorough evaluation to identify contraindications for testosterone therapy. Locally advanced or metastatic prostatic cancer, male breast cancer, men with an active desire to have children, having Hematocrit > 54%, and untreated or poorly controlled congestive heart failure are considered contraindications of TRT. Precaution should also be considered before prescribing testosterone in men with severe lower urinary tract systems, baseline hematocrit of 48-50 %, and a familiar history of DVT (36).

Table 1: outlines the various administration methods for TRT and their characteristics. There are various formulations and usage ways for TRT in hypogonadal men, including topical usage (gel and solution), long-acting and short-acting injections, tablets, capsules, subcutaneous testosterone implants with different dosages based on the type of testosterone and its brand (45). Selecting the optimal TRT method remains challenging. Studies have evaluated the efficacy of different testosterone formulations in treating male hypogonadism. Notably, intramuscular injections appear to minimize the risk of prostate cancer to other preparations (24). European Association of Urology Guidelines on Sexual and Reproductive Health recommends regular evaluation for men receiving TRT. Clinicians should assess clinical symptoms of LOH, and anthropometric parameters (mainly BMI and WC), perform digital rectal examinations, and monitor blood pressure. Additionally, hematocrit (Hct) levels should be measured 3 to 6 months after initiating testosterone therapy and then annually. If Hct exceeds 54%, TRT should be temporarily stopped until levels normalize. All TRT patients should also be evaluated for hypoxia and sleep apnea (36).

2.2. Erectile dysfunction

ED, which affects millions of men worldwide, is characterized by the consistent or recurrent inability to achieve and/or maintain a penile erection for sexual satisfaction. ED has various origins, including organic, psychogenic, and mixed etiologies (46). The main risk factors associated with this prevalent sexual dysfunction include aging, medical conditions such as diabetes mellitus, dyslipidemia, hypertension, metabolic syndrome (MetS), CVD, obesity, hyperhomocysteinemia, lack of exercise, smoking, alcohol use, and receiving pharmacotherapeutic agents for CVD (47).

Earlier studies have demonstrated a significant link between ED and an increased risk of cardiovascular events, including myocardial infarction, cerebrovascular events, and all-cause mortality, with an upward trend in mortality due to CVD (47, 48). Notably, both ED and CVD share systemic vascular disease as their etiology, emphasizing common risk factors (49). Consequently, ED may serve as an early sign of coronary artery disease (CAD) and peripheral vascular disease, extending beyond mere sexual and psychological concerns. ED can be considered a potential warning sign for further CVD issues

Table 1: Administration ways of testosterone replacement therapy and specific features of each method

Administration ways	Benefits	Drawbacks
1 Topical a. Transdermal topical testosterone gel b. Testosterone solution Note: Applied in the axillae once a day	– Easy application with an acceptable skin tolerability – creating a normal range of testosterone for 24 hours – Adjustable dose when needed.	– Skin dryness and irritations – Time-consuming to apply – Transferring drug to partner through skin-to-skin contact – Increased concentrations of dihydrotestosterone (DHT) due to the presence of 5-reductase in the skin
2 Long-acting testosterone injections (deep injections every 10-14 weeks into a gluteal muscle)	– Maintaining physiological serum levels of testosterone for 3 months or longer – Effective and convenient	– Injection pain, inconvenience, and reaction – Needs to inject by another person – Lack of adjustable dose when adverse effects happen
3 Short-acting T injections (every 2–4 weeks IM or SC)	– Flexibility in administration – Not expensive – Effective on testosterone deficiency symptoms – Relatively safe and tolerable	– Increased risk of polycythemia – Pain and tenderness at injection place – Needs to be injected by another person
4 Tablets (actually twice daily)	– Convenient to apply – Effective –	– Taking time to use – Forgetting the use – Takes time to get used to; patient education is vital for medication adherence. – Risk of a gum-related adverse event when tablets applied to the upper gum
5 Subcutaneous T implants (Testosterone pellets 100 or 200 mg to a total of 600–1200 mg testosterone per dose (a rare administration way)	– Serum concentrations of testosterone reach the highest level at 1 month and are sustained in the normal range for up to 6 months – Convenient to apply (twice or thrice a year application)	– Painful procedure – Increased risk of infection – Skin scar tissue – Risk of spontaneous extrusion after implantation
6 Oral capsules (1–3 capsules twice or thrice daily with meals)	– Easy to apply – Appropriate for patients who cannot tolerate other forms of treatment	– Low bioavailability and inter-and intra-variability in effectiveness – Normal serum T level attained for only up to 3–5 h

Abbreviations: IM: intramuscular; SC: subcutaneous; h: hour

(49, 50). Given that ED is one of the most prevalent sexual dysfunctions in men, early diagnosis and effective management of this disorder can significantly enhance their quality of life and contribute to a satisfactory sexual relationship (36, 51, 52).

2.2.1. Screening and diagnostic evaluation of erectile dysfunction

A diagnosis of ED can be made by a primary care physician. All men with ED signs should undergo careful screening to establish a definitive diagnosis. Obtaining a detailed medical and sexual history is essential during the evaluation of these individuals. Factors such as stress, cultural background, and the patient's cognitive/thinking style regarding sexual performance may significantly influence erectile function. Therefore, Men with ED should be thoroughly assessed for these predisposing factors. To diagnose ED, it is recommended to use a validated and reliable questionnaire (36, 51). The International Index of erectile function (IIEF) is a well-known multidimensional scale which widely used to identify cases of ED. Additionally, the IIEF can assess the efficacy of treatments (53). A comprehensive physical examination should also be included in the primary assessment of men with ED to rule out medical conditions and genital disorders related to this dysfunction (36, 51). Laboratory tests, including fasting glucose, lipid profiles, and total testosterone, can help to identify modifiable risk factors associated with ED (36).

2.2.2. Pharmacological approaches for erectile dysfunction

The question of whether ED is curable remains a challenge. While several therapeutic options can successfully manage ED, it cannot be fully cured except in specific cases with etiologies such as psychogenic factors, post-traumatic arteriogenic conditions in young patients, or hormonal causes, specifically hypogonadism (36). Among the pharmacological agents prescribed for ED, PDE5Is, TRT, topical/ intraurethral alprostadil, and intra-cavernous injection therapy are considered the most common treatment strategies (39, 54-56).

2.2.2.1. Phosphodiesterase type 5 inhibitors for erectile dysfunction

PDE5Is are recognized as the most satisfying and the first-line therapeutic option (57). During a penile erection, cyclic guanosine monophosphate (cGMP) is metabolized via the PDE5 enzyme, preventing its downstream erectile effects.

PDE5Is competitively reduce cGMP metabolism, leading to achievement and maintenance of an erection (58). These PDE inhibitors decrease cGMP hydrolysis in the cavernosal tissue, resulting in smooth muscle relaxation and increased arterial blood flow. This process compresses the subclinical venous plexus, leading to a penile erection (59). In 1998, sildenafil (Viagra), a PDE5I, received FDA approval as the first oral treatment for ED. Other PDE5I products, including tadalafil (Cialis), vardenafil (Levitra), and avanafil (Stendra), are currently used for managing patients with ED (58). A network meta-analysis, encompassing RCTs, has robustly demonstrated that PDE5Is are both effective and safe for over 80% of patients with ED when compared to placebo (27). PDE5I regimens are often on-demand, daily, or a combination of on-demand and daily methods (57). While data on the superiority of combination approaches remains limited, a recent study highlighted the benefits of combining tadalafil (5 mg daily) with sildenafil (50 mg on demand) (60). Current evidence supports that all PDE5Is are generally well tolerated and safe. However, they may be associated with specific adverse effects, including headache, dizziness, flushing, dyspepsia, nasal congestion or rhinitis, myalgia, anterior optic neuropathy, and hearing loss. Importantly, the occurrence of these adverse effects depends on the dose and specific drug (61). A comprehensive network meta-analysis of 179 RCTs demonstrated the efficacy of PDE5I compared to placebo. Notably, sildenafil (25-50 mg) exhibited superior effectiveness in improving erectile dysfunction as measured by the IIEF. Meanwhile, tadalafil (10-20 mg) also demonstrated favorable profiles. However, avanafil was less effective than other interventions. This meta-analysis also assessed safety across different PDE5I compounds. Mirodenafil (150 mg) was significantly associated with more adverse events, particularly flushing and headaches. Sildenafil (100 mg) revealed a stronger association with visual disorders, while vardenafil was linked to nasal congestion (27). Another meta-analysis, based on 1056 records from 15 RCTs specifically explored PDE5Is efficacy in managing ED diabetic men. The results indicated that on-demand administration of vardenafil and sildenafil appeared to be more efficient and had fewer adverse effects compared to other compounds. Notably, there was no significant difference between regular and on-demand regimens of PDE5Is (59). It is crucial to emphasize patient education as a critical component of successful ED management. Patients should take PDE5Is 30- 60 minutes before engaging in sexual intercourse, as specified by the formulation. It is essential to emphasize that both mental and physical stimulation are necessary for achieving satisfactory sexual function. PDE5Is enhance the body's natural response to sexual arousal. Patients should be aware that psycho-emotional factors, such as stress and anxiety, can impact the effectiveness of PDE5Is. Addressing these distresses is crucial for optimal outcomes. Before concluding treatment failure, it is advisable to try at least two different PDE5Is. Individual responses can vary, and an alternative medication may yield better results. PDE5Is are contraindicated in specific patient groups, including those receiving antihypertensive medications, individuals using organic nitrate products, such as nitroglycerine, and patients with a history of receiving other nitrate preparations in managing angina and recent CVD (62).

2.2.2.2. Alprostadil (topical and intraurethral) for erectile dysfunction

Alprostadil, a second-line treatment option for ED, is prescribed either alone or in combination with PDE5Is (56). This synthetic analog of prostaglandin E1 (PGE1) closely resembles naturally occurring PGE1. It binds to G protein-coupled PGE1 receptors concentrated on the surface of smooth muscle cells, therefore activating cAMP (cyclic adenosine monophosphate), which in turn induces penile vascular smooth muscle relaxation to create a normal penile erection (63). Topical and intraurethral alprostadil administration is considered highly effective for men with ED, yielding a relatively high response rate (64, 65). In the topical route, a cream is applied through a permeation enhancer to facilitate absorption of alprostadil (200-300 mg) is applied with a permeation enhancer to facilitate absorption via the urethral meatus. Intraurethral insertion of alprostadil (125–1000 mg) using a medicated pellet (MUSE) is a direct approach that appears more effective than the topical form (66). These medical agents may be associated with adverse effects such as penile pain, erythema, burning, dizziness, and hypotension (36, 66). Notably, an NRS involving 170 patients with ED demonstrated greater effectiveness when combining topical alprostadil with PDE5I, without increasing the adverse effects of the therapy (28). Alprostadil serves as an alternative for individuals who are reluctant to take systemic treatments or have contraindications for PDE5Is. It is also suitable for patients who do not respond well to or cannot tolerate other treatments (65). Alprostadil can be administrated via intracavernous injections with a dose ranging from 5 to 40 mg. This approach is recognized as one of the most efficacious monotherapy methods in men with ED. However, it is worth noting that some patients may hesitate due to the fear of penile puncture. While alprostadil is a viable therapeutic option for ED, it is essential to consider potential adverse effects. Prolonged, undesired erections can occur with alprostadil use. Clinicians should carefully assess patients receiving this medication to monitor for this complication. Alprostadil treatment may be associated with fibrotic changes. Vigilance is necessary to detect any signs of tissue fibrosis. Some individuals may experience mild hypotension (low blood pressure) as a side effect of alprostadil. Alprostadil should be avoided in patients with a history of hypersensitiv-

ity to the drug. Men at risk of priapism (e.g., those with sickle cell disease or certain anatomical conditions) should exercise caution. Alprostadil use is not recommended for men with bleeding disorders (36). In clinical practice, a thorough assessment of individual patient profiles is crucial to ensure safe and effective use of alprostadil.

2.2.2.3. Testosterone replacement therapy for erectile dysfunction

TRT (intramuscular or transdermal) represents an additional therapeutic avenue for managing ED. This approach is particularly relevant for individuals with low or low-normal serum concentrations of testosterone, especially when there is a clear association with sexual function, including sexual desire and erectile capacity. Notably, patients with specific hormonal abnormalities should be promptly referred to an endocrinologist for comprehensive evaluation (36). A meta-analysis of 14 studies involving 2,298 men demonstrated that testosterone therapy significantly improves erectile function and other sexual parameters. The findings underscore the significant improvement in erectile function and other sexual parameters following TRT. This observation reinforces the notion that sexual dysfunction often serves as a hallmark manifestation of testosterone deficiency. For hypogonadal men experiencing milder degrees of erectile dysfunction, TRT alone may be a reasonable treatment choice. Conversely, in cases of more severe ED, combination therapy—such as the addition of PDE5Is—may be more appropriate (67). In summary, individualized assessment, consideration of hormonal status, and tailored treatment strategies are pivotal in optimizing outcomes for men with ED.

2.3. Premature ejaculation

PE is one of the most prevalent sexual dysfunctions in men, with a wide-ranging prevalence estimated between 30- 75%. However, diagnosing this condition poses challenges due to the absence of a universally accepted definition (68, 69). According to EAU guidelines 2021, PE—whether lifelong or acquired— is characterized by ejaculation that always or nearly always happens before or within about 1 min of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 min (acquired PE); the inability to delay ejaculation in all or nearly all vaginal penetrations; negative personal consequences, such as distress, bother frustration, and/or the avoidance of sexual intimacy (36). The International Society for Sexual Medicine (ISSM) has also contributed recommendations aimed at refining the scientific definition of PE. According to these recommendations, lifetime PE (primary PE) was defined as ejaculation that always or almost always occurs before vaginal penetration or within about 1 minute of the first sexual experience. Acquired PE (secondary PE) has been defined as a clinically significant and disturbing reduction in ejaculation time, and an inability to DE, typically within 3 minutes or less (70). The pathophysiological mechanism underlying PE remains intricate and not fully elucidated. PE tends to be more prevalent among older men, in particular those with conditions such as diabetes, hypertension, hyperthyroidism, alcoholism, substance abuse, and sleep disorders. Depression, stress, anxiety, and traumatic sexual experiences may also trigger or exacerbate PE (71). In summary, understanding the multifaceted nature of PE requires a holistic approach, considering both physiological and psychological aspects.

2.3.1. Screening and diagnostic evaluation of premature ejaculation

Clinicians should meticulously evaluate all men presenting with PE symptoms or those at risk for this disorder. While a definitive test for identifying PE remains elusive, a comprehensive evaluation involving detailed medical history and physical examination is crucial. The diagnosis of PE should adhere to international guidelines for the diagnosis of sexual dysfunctions (68, 71).

2.3.2. Pharmacological approaches for premature ejaculation

Pharmacological interventions play a substantial role in managing PE. The choice of therapy depends on whether the PE is lifelong or acquired, and a comprehensive evaluation is essential to guide treatment decisions. These agents should be considered as the first-line therapy for men with lifelong PE (72). Concurrently, evaluation and management of medical conditions such as prostate and lower urinary tract disorders, psychological problems, and endocrine disturbances, especially diabetes and hyperthyroidism must be the main objective for men with acquired PE (36, 59).

A wide range of pharmacotherapy agents has been suggested to manage PE. Among these agents, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and topical anesthetic approaches are considered the most common therapeutic approaches (36). The AUA/SMSNA guideline (2021) recommends paroxetine, clomipramine, sertraline, fluoxetine, and citalopram as first-line options, while tramadol, terazosin, alfuzosin, silodosin, and doxazosin serve as the second-line choices. Pharmacotherapies for PE can be administrated either at a scheduled or on demand, depending on the formulation and dosage (73). PDEIs, either alone or in combination with other drug groups, have been demonstrated to have acceptable efficacy in treating PE (29-31, 59, 74). A meta-analysis of 5 publications involving 419 patients demonstrated that PDE5-Is combined with SSRIs significantly improve ejaculatory latency time compared to SSRIs alone in primary PE (30). In diabetic men, a network meta-analysis of 15 RCTs (involving 5274 patients) highlighted the effectiveness of PDE5I administrations. On-demand usage of vardenafil and mirodenafil was associated with better efficacy and fewer side effects, while no significant difference

was observed between regular and on-demand PDE5Is regimens (59). Another network meta-analysis, which included 44 RCTs involving 11,008 patients, highlighted the efficacy of combining SSRI with PDE5I as the most effective treatment for PE. While topical anesthetics were also found to be highly effective, concerns persisted regarding their potential adverse effects, which could not be adequately assessed. Additionally, tramadol, despite its significant impact on PE, was associated with strong addictive properties (31).

Finally, it is essential to note that international guidelines do not recommend solely behavioral techniques for lifelong PE. Instead, pharmacotherapy should be considered a substantial component of the therapeutic approach. Furthermore, in cases of acquired PE, a combination of behavioral therapy and pharmacological interventions may yield the most effective results when compared to solely medical treatment (36).

3. Conclusions

This review provides a comprehensive overview of standard diagnostic evaluation and treatment of male sexual dysfunctions, with a focus on pharmacological interventions, aiming to a balance between efficacy and safety. While existing literature offers valuable insights, our review underscores the need for precise evaluation before prescribing these medical agents to identify real indications of the treatment. Clinicians should consider individual patient characteristics, potential adverse effects, and evidence-based recommendations when selecting the most appropriate treatment.

4. Appendix

4.1. Acknowledgment

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4.2. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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None.

4.4. Authors contributions

M.A., Study conceptualization, literature search, data collection, critical discussion, drafting, and revising the manuscript; M.N, F.A, and T.P.N, reviewing and editing the manuscript; and F.R.T, critical discussion, and editing the manuscript.

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