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Review Article

Emerging Treatments For Erectile Dysfunction

A Novel Method for Identifying and Treating Erectile Dysfunction

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Abstract: Sexual or erectile dysfunction (ED) is the ineptitude to get or keep a hard penile erection. ED can have a detrimental effect on physical and psychological health. This review helps in understanding the detailed etiology of ED and various approaches for the management of ED. The occurrence and incidence of erectile dysfunction are on the rise among men. Various other factors greatly impact the progression of ED, including individual general health and physiological conditions such as psychiatric or psychological problems, diabetes mellitus, genitourinary disease, cardiovascular disease, and chronic diseases. Erectile dysfunction occurs when the release of nitric oxide (NO) triggers the activation of the guanylate cyclase enzyme in the spongiosum and corpora cavernosa, leading to relaxation of the vascular smooth muscle and an increase in cyclic guanosine monophosphate (cGMP) levels. This physiological process is essential for achieving and maintaining a firm penile erection. Some common and advanced methods, such as the physical method, sexual history, laboratory testing, apomorphine test, NPTR test, and color duplex Doppler ultrasound test, are used to diagnose erectile dysfunction. This review also focuses on emerging treatments that address the medical need for effective ED management. This comprehensive review bridges gaps in the current literature, offering superior insights into ED management and improving the quality of life for individuals with ED.

Keywords: Erectile dysfunction; Nanotechnology; penile erection; emerging treatment; management of ED; NPTR test.

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1. INTRODUCTION

Erectile dysfunction (ED) is a widespread condition that affects a significant number of men globally. It is characterized by the inability to achieve or maintain a firm erection for satisfactory sexual intercourse, leading to frustration, dissatisfaction, and potential strain on relationships [1]. The incapability to obtain or keep a hard penile erection for enjoyable sexual interaction is called erectile dysfunction (ED) [2]. The origins of erectile dysfunction (ED) are typically attributed to its pathophysiology, which could be categorized as endocrinologic, vasculogenic, neurogenic and psychogenic, or drug-induced [3]. Due to its detrimental effect on both physical and psychological health, it can significantly affect patients' satisfaction as well as of their mates. It has been observed through epidemiological studies that the occurrence and incidence of erectile dysfunction are rising among men [4]. Data from the epidemiological studies concludes that approximately 35% of men aged above 60 and 50% above 70 yrs are diagnosed with ED[5]. It has been estimated that this condition affects approximately 150 million individuals globally [6]. Furthermore, findings from the ENIGMA study conducted in 2004 indicated a prevalence of approximately 17% among European men [7]. The study of erectile dysfunction has a rich history, dating back to early research exploring its physiological and psychological aspects. Previous studies have provided valuable insights into the vascular, neurological, hormonal, and psychological factors contributing to ED. However, these early research endeavors often lacked a comprehensive and integrated approach, focusing predominantly on a single aspect or limited treatment modalities [8]. Erectile dysfunction (ED) commonly coexists with medical conditions such as hypertension, diabetes mellitus, obesity, and atherosclerosis [9]. One of the significant limitations encountered in the early research on erectile dysfunction (ED) was the fragmented understanding of the condition. Previous studies often focused solely on physiological or psychological factors, neglecting the intricate interplay between these domains. Consequently, the available treatment options were frequently limited and failed to address the underlying causes of ED effectively. Consequently, there is a pressing need to develop a more comprehensive and innovative approach to identify and treat erectile dysfunction [10] accurately. Despite advances in the field, erectile dysfunction remains a significant health concern with a profound impact on the quality of life for affected individuals and their partners. Existing treatment approaches, such as oral medications, injections, and devices, have limitations and do not adequately address the condition's root causes. Therefore, there is a pressing need for a novel method that integrates the latest scientific findings to provide a comprehensive and personalized approach to identifying and treating erectile dysfunction [11]. The individual's general health and non-communicable diseases such as psychiatric/psychological problems, diabetes mellitus, genitourinary disease, cardiovascular disease, and chronic diseases are some major risk factors linked to erectile dysfunction [12]. Mazzilli et al. (2022) proposed a methodology for investigating and evaluating erectile dysfunction. This approach involves conducting a thorough anamnestic inquiry that focuses on several aspects, including the time of onset of ED, interaction with a specific partner, degree of erection/rigidity, presence of couple discord, ejaculation without an erection, and occurrence of nocturnal sudden erections. Additionally, specific questionnaires such as the IIEF 15 may be utilized to determine the total score for ED, which should be less than 26. Alternatively, the IIEF 5 questionnaire with a total score of less than 22 may be used, indicating ED. Specialized first-level studies, including biochemical and hormone tests, and second-level studies, such as the study of the neurogenic reflex, penile color Doppler, and monitoring of nocturnal penile erections, may also be necessary to diagnose and assess the condition [13] accurately. Raheem et al., (2021) have given noble techniques for managing erectile dysfunction, such as stem cell therapy and platelet-rich plasma [14]. This review proposes a novel approach to identifying and treating erectile dysfunction by addressing research gaps. Vardenafil and tadalafil, newer medications than sildenafil, provide alternative treatment options. They differ in their chemical structures, particularly in ring configurations. Vardenafil's structural modifications enhance its binding to PDE-5, while tadalafil replaces the piperazine ring with a hydantoin ring. Clinical trials show a strong preference for tadalafil over sildenafil in men with erectile dysfunction[15]. The review article's findings and recommendations hold promise for transformative shifts in diagnosing and treating erectile dysfunction. Overcoming research limitations and adopting comprehensive approaches enable tailored interventions, potentially enhancing outcomes, patient satisfaction, and long-term understanding. This study also fosters further research and innovative strategies, revolutionizing erectile dysfunction management [16]. This review article introduces a pioneering approach to diagnosing and treating erectile dysfunction by integrating current scientific knowledge and addressing research limitations. It Aims to review etiology and pathophysiology, identify research gaps, propose a new framework, and discuss the potential impact and future directions.

2. SCIENTIFIC RATIONALE

An erection involves vascular, neural, endocrine, and psychological factors. Sensory inputs from visual, olfactory, imaginative, and genital stimulation are integrated into the brain. 5-HT, Dopamine, Norepinephrine, and oxytocin are neurotransmitters that attach to receptors in the penile nerves. Dopamine induces erections indirectly via the D1 and D2 receptors [17]. Activating oxytocinergic neurons that release oxytocin, 5-HT has inhibitory effects on erections, with 5-HT1A inhibiting erection and facilitating ejaculation, while 5-HT1C stimulation induces erection [18, 19]. Melanocortins interact with MC3R and MC4R, impacting dopaminergic neurons and activating the NO/cGMP pathway, leading to oxytocin release [20]. The spinal cord, brain, and penile nerves receive the pro-erectile signal from melanocortins[21]. The sacral erection center comprises neurons in the spinal cord and cavernous nerves. Nonadrenergic-noncholinergic fibers release nitric oxide (NO) in the penis upon acetylcholine stimulation. NO activates sGC, increasing cGMP synthesis, inducing smooth muscle relaxation, and enhancing blood flow [22, 23]. The cGMP pathway is essential for erection, while cAMP has a supportive role [24]. Adenosine stimulates AC, generating cAMP and activating cAMP-dependent kinase (cAK). cAK phosphorylates targets in the downstream pathway, regulating specific functions [25].

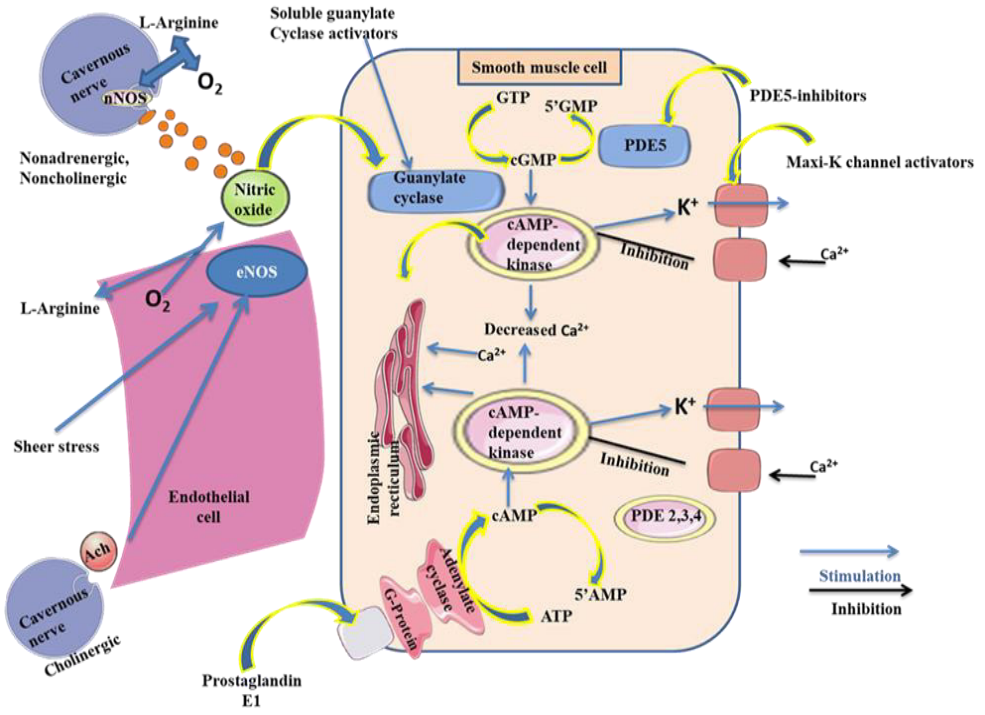

Fig. 1: - Molecular pathways that play a role in the relaxation response of penile smooth muscle [23].

(Fig. 1) Illustrates the key molecular pathways engaged in the relaxation of penile smooth muscle. Activation of soluble guanylate cyclase (sGC) leads to increased cyclic guanosine monophosphate (cGMP) levels, which activate a specific protein kinase. This kinase inhibits intracellular calcium influx, resulting in smooth muscle relaxation. Additionally, cAMP contributes as a supporting factor in this process. Understanding these molecular mechanisms is crucial for elucidating the physiological basis of erectile function and developing targeted therapies for erectile dysfunction. Sympathetic adrenergic nerves primarily regulate the flaccid state and subsiding of the erect penis from sexual arousal. Norepinephrine stimulates α1-adrenoceptors, which contract the smooth muscle in penile trabeculae and arteries [26, 27]. This contraction involves the mobilization of intracellular calcium ions (Ca2+), which bind to calmodulin, activating myosin light-chain kinase (MLCK). MLCK phosphorylates myosin, initiating smooth muscle contraction. Reversal of contraction occurs through dephosphorylation of myosin light chain (MLC) MLC phosphatase (MLCP) - Phosphorylation-regulating enzyme for myosin light chain (MLC) RhoA/Rho-kinase (ROCK) pathway - RhoA signaling pathway involving Rho-kinase, activated by RhoA, inhibits MLCP, sustaining smooth muscle contraction [28, 29]. The ROCK pathway also influences cavernosal endothelial cell integrity and function and may be involved in apoptosis [30].

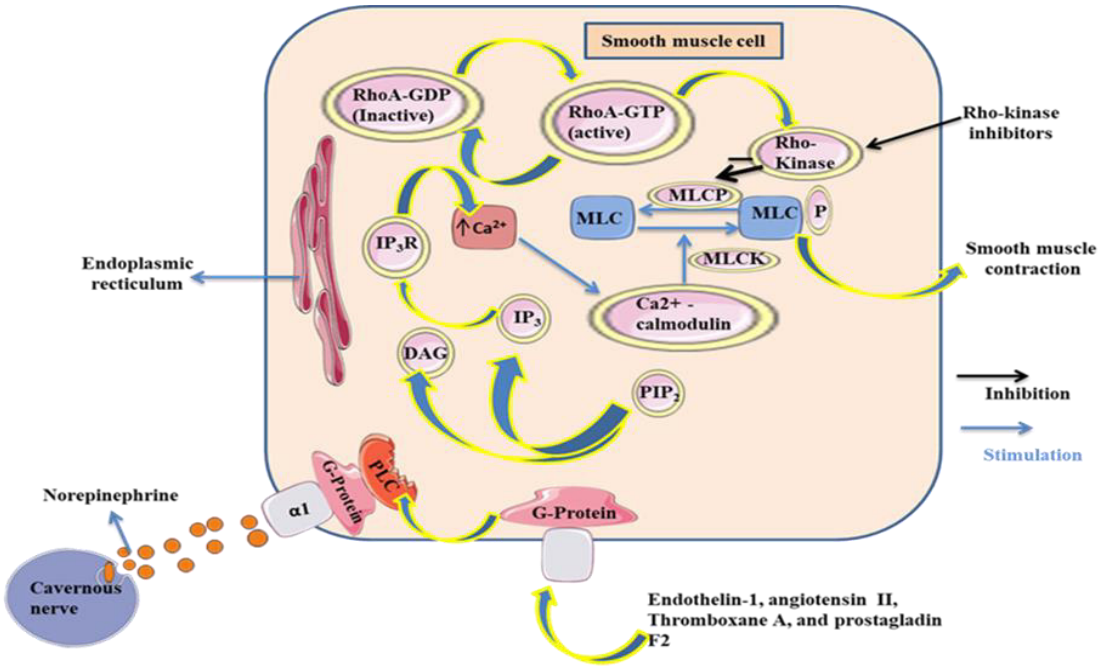

Fig 2: Molecular mechanisms implicated in the constriction of smooth muscle in the penis. [31]

Angiotensin II, prostaglandin F2, endothelin-I, and thromboxane A2 bind to G-PCR receptors, which activate phospholipase C which in turn hydrolyses phosphatidylinositol 4,5-bisphosphate to produce 1,2-diacylglycerol (IP3) and 1,4,5-triphosphate. IP3 adheres to dedicated (IP3R) on the smooth endoplasmic reticulum, releasing intracellular calcium stores [22]. These vasoconstrictor agonists can bind to receptor-activated channels and release the stored calcium without changing membrane potential (Fig. 2) [31]. Potassium channels in the smooth muscle of the cavernosal tissue play a crucial role in regulating erections. These channels come in various types. The most significant contributors are the participation of the (maxi-K), which are calcium-sensitive, and (K ATP) channels, which are controlled metabolically. Activation of these channels leads to hyperpolarization of the smooth muscle cells, resulting in the closure of voltage-dependent calcium channels. Consequently, the concentration of intracellular free calcium decreases, leading to the relaxation of the cavernosal smooth muscle.

3. CURRENT RESEARCH GOALS

Ongoing research in erectile dysfunction (ED) drug development focuses on three main areas: enhancing the selectivity and effectiveness of current PDE5 inhibitors (PDE5-Is), exploring alternative signaling pathways underlying the erectile response, and advancing gene-related treatment strategies. Multiple FDA-approved PDE5-Is are available, and both existing international options and newly developed compounds show promising outcomes in clinical trials. Researchers are investigating the central modulation of dopamine, serotonin, and melanocortin receptors, while also exploring peripheral approaches targeting pathways upstream of NO-dependent activation of sGC. Additionally, the Rho-kinase pathway has shown potential through its antagonism in inducing penile erections. Gene therapy has gained attention, with direct injection of genetic material into the easily accessible penis, utilizing the slow turnover rate of the tunica albuginea for prolonged effects [32]. Initial clinical studies utilizing the Maxi-K ion channel for gene transfer have demonstrated encouraging results and a favorable safety profile [33].

4. ANATOMY AND PHYSIOLOGY OF ERECTION

The neurological, circulatory, and endocrine systems are all involved in the multifactorial, complex pathway that leads to erectile dysfunction. Understanding the pathophysiology and the reasoning behind treatment options will be made easier with a complete understanding of the anatomy and physiology of erections (Fig. 3). The penis comprises the corpora cavernosa, which passes through the corpus spongiosum and encircles the urethra along the entire length of the penile shaft. The peripheral nervous system's somatic (sensory and motor) and autonomic (sympathetic and parasympathetic) branches supply the penile tissue. The sympathetic nerves, which have an anti-erectile effect and regulate ejaculation and detumescence, emerge from T11-L2. On the other hand, the parasympathetic nerves that support erection arise from S2-S4. To maintain blood flow during an erection, cavernous sympathetic and parasympathetic nerves infiltrate the corpus spongiosum, corpora cavernosa, and glans penis [34].

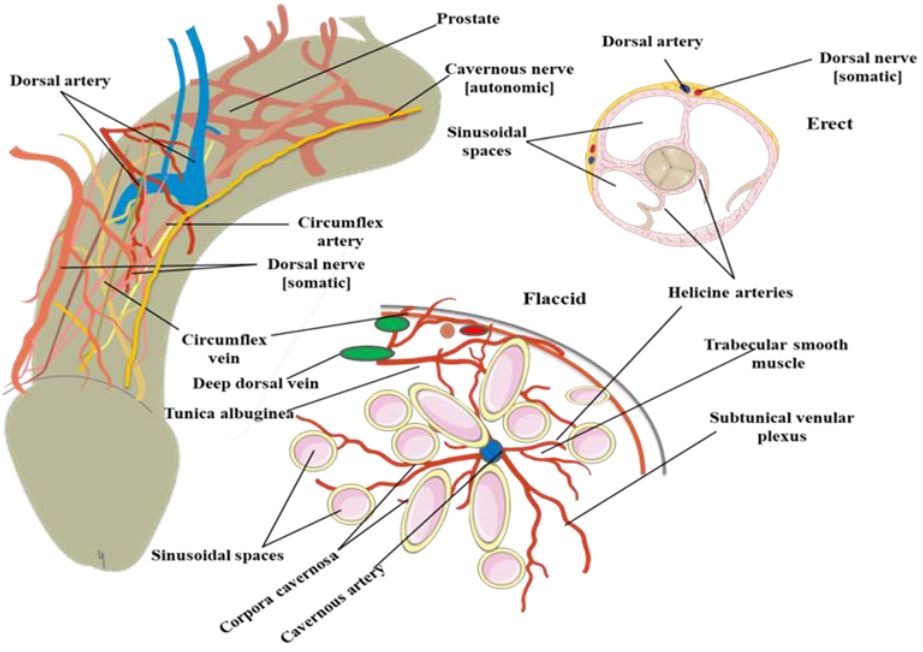

Fig 3: - Anatomy and Mechanism of Penile Erection, displaying the main structures, blood vessels, and nerves [35].

The autonomic cavernous nerves regulate penile blood flow during erection, while the somatic dorsal nerves are responsible for penile sensation. During an erection, smooth muscle relaxation and arteriolar vasodilation increase blood flow, expanding sinusoidal spaces and enlarging the penis. The expanded sinusoids compress the subtunical venular plexus against the tunica albuginea, reducing blood outflow. In the flaccid state, minimal inflow occurs through constricted helicine arteries, with free outflow via the subtunical venular plexus. The pudendal nerve gives motor capability to the pelvic floor, sphincters, stiffness muscles, and sensibility to the pelvis. The penis receives blood from the internal pudendal arteries, which divide into the bulbourethral, cavernosal, and dorsal arteries. The bulbourethral artery

supplies blood to the bulb of the penis and the penile urethra and runs through the deep penile fascia.

Meanwhile, the dorsal artery gives off circumflex branches that support the veins and terminate in the glans, passing between the deep dorsal vein and the dorsal nerve. The deep penile or cavernosal artery supplies the specialized helicine arteries, which extend the length of the penile shaft and enter the corpus cavernosum at the crus [36]. Acetylcholine (Ach) is released by parasympathetic nerves in response to sexual stimulation (Fig. 4). Nitric oxide (NO) is produced within the endothelial cells lining penile arteries through the action of nitric oxide synthase (eNOS), which converts L-arginine into NO. The guanylate cyclase enzyme in the spongiosum and corpora cavernosa is activated by releasing NO, producing cGMP (cyclic guanosine monophosphate), and relaxing the vascular smooth muscle [37, 38].

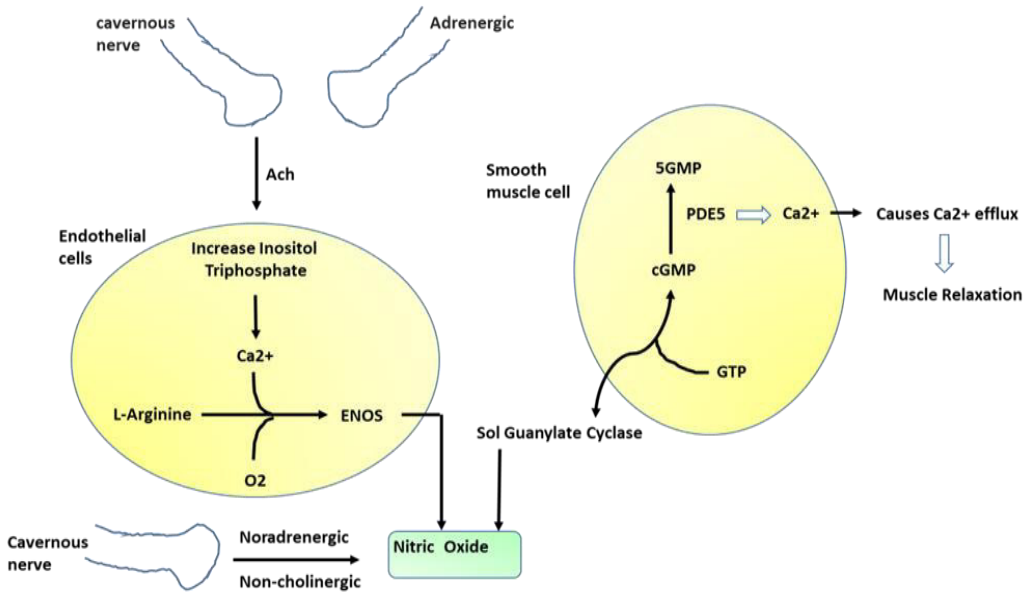

Fig 4: Physiology of Erection of penis [39].

The diagram depicts the process of sexual stimulation triggering the release of (Ach) liberated by the parasympathetic neural pathways, leading to the conversion of L-arginine into nitric oxide (NO) by nitric oxide synthase (eNOS) in endothelial cells. This NO release then activates guanylate cyclase, which increases cyclic guanosine monophosphate (cGMP) levels. Elevated cGMP levels subsequently relax the vascular smooth muscle in the spongiosum and corpora cavernosa, ultimately leading to penile erection. Understanding the role of NO in erections is important in developing effective treatments for erectile dysfunction.

5. PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

ED is categorized into a combined psychogenic and organic form (drug-induced or neurogenic, hormonal, arterial, and cavernosal). The assorted psychogenic and organic form is the most prevalent. "The causes of ED can be complex and varied. Depression, relationship problems, anxiety, and stress are some psychological factors that describe the fear of erectile dysfunction can all contribute to the condition. Neurological factors such as central or peripheral neurologic disease can also be a cause. Hormonal changes, particularly decreased testosterone levels, can lead to erectile dysfunction. Vascular pathologies, including hypertension and atherosclerosis, can negatively affect blood flow and contribute to the condition [40]. Certain conditions, such as cardiovascular disease, hyperlipidemia, diabetes, chronic kidney disease, and reproductive cancer, can also prompt erectile dysfunction. It is important for individuals experiencing erectile dysfunction to consult with a healthcare professional to determine the underlying cause and appropriate treatment options [41]. The following factors are responsible for erectile dysfunction **(**Fig. 5).

6. CAUSE OF ERECTILE DYSFUNCTION

The causes of ED can be complex and varied. Psychological factors such as anxiety, stress, depression, relationship problems, and fear of erectile dysfunction can all contribute to the condition. Neurological factors such as central or peripheral neurologic disease can also be a cause. Hormonal changes, particularly decreased testosterone levels, can lead to erectile dysfunction. Vascular pathologies, including hypertension and atherosclerosis, can negatively affect blood flow and contribute to the condition[13]. Certain conditions, such as cardiovascular disease, hyperlipidemia, diabetes, chronic kidney disease, and reproductive cancer, can also prompt erectile dysfunction. It is important for individuals experiencing erectile dysfunction to consult with a healthcare professional to determine the underlying cause and appropriate treatment options [14]. The following factors are responsible for erectile dysfunction (Fig. 3).

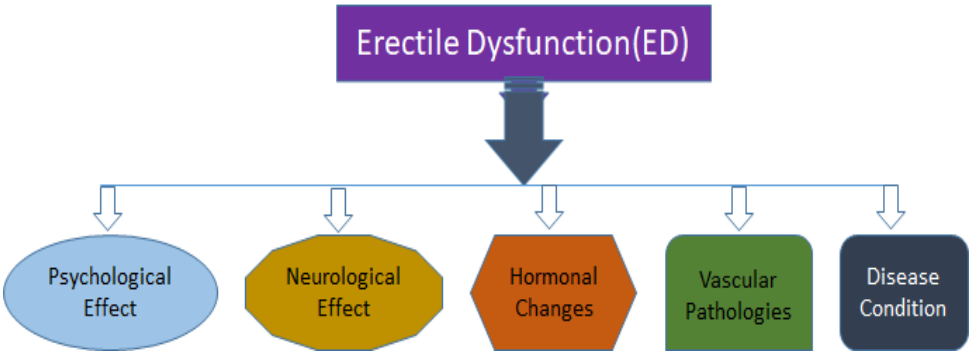

Fig. 5 :- The causative factors of Erectile dysfunction [42]

Various factors, including psychological effects such as anxiety, stress, depression, relationship problems, fear, neurological effects, hormonal changes, vascular pathologies, and disease conditions, can cause erectile dysfunction. Understanding these factors is crucial for effective diagnosis and treatment of erectile dysfunction.

7.1. Psychological effect

Psychological factors contributing to erectile dysfunction are not as simple to detect, diagnose and treat. The most common psychological factors for ED are as follows [43, 44].

7.2. Anxiety

Real, tangible bodily ramifications of psychological problems. For instance, many people believe that they don't experience anxiety. However, anxiousness can result in a faster heartbeat, problems with blood pressure, and exhaustion. As a result, anxiety can impact sexual performance and is ED's most prevalent psychological cause.

7.3. Stress

Everybody experiences stress once or twice in their lives. Stress can occasionally serve as a potent motivator. The capacity to achieve and maintain sexual performance might be affected by stress.

7.4. Depression

An imbalance in brain chemistry is frequently the root cause of depression. Both sexual desire and sexual performance may be impacted.

7.5. Relationship problem

Suppose there is a bad relationship between the partners. Sexual relationships can be impacted by problems in a couple's relationship. Fury, poor communication, and arguments can affect sexual function and desire.

7.6. Fear of erectile dysfunction

First-time people experiencing erectile dysfunction; may become nervous that they will never recapture normal sexual function. This can steer to fear. Psychological factors such as stress, anxiety, depression, relationship issues, and fear can affect a person's ability to achieve or sustain an erection during sexual activity. These emotions may play a role in the onset of erectile dysfunction.

7.7. Neurological effect

Neurogenic erection dysfunction is caused by neurological factors mentioned in Table- 1. The incapability to attain or regulate erectile dysfunction caused by either central or peripheral neurological diseases can result in difficulty achieving or maintaining an erection [45].

Table- 1: List of Neurological factors that cause erectile dysfunction

Sr. no.	Neurological factors	Cause	References
1	Spinal cord injury	Due to spinal cord injury, organic changes occur in men, and these changes cause erectile dysfunction.	46
2	Cerebrovascular accident	Acute ischaemic stroke in the brain causes erectile dysfunction.	47
3	Parkinson's disease (PD)	Erectile dysfunction can occur in people with Parkinson's disease due to testosterone deficiency.	48
4	Multiple sclerosis	Erectile dysfunction is the primary autonomic nervous system disease associated with a persistent disease that affects the myelin sheath surrounding nerve fibers in the central nervous system (CNS) and is known as demyelinating disease.	49
5	Epilepsy	Epilepsy is the common cause of erectile dysfunction.	40
6	Lumbar disc herniation (LDH)	LDH, a pathological condition, commonly causes radicular pain. Lumbosacral disc disease can affect nerve conduction related to erection through various somatic and autonomic pathways.	50

Table- 1. Represents various neurological conditions and their association with erectile dysfunction. Spinal cord injury, cerebrovascular accident, Parkinson's disease, multiple sclerosis, epilepsy, and lumbar disc herniation are discussed as potential causes of erectile dysfunction due to organic changes or disruptions in neurological pathways. This

comprehension can be beneficial for healthcare professionals to recognize and manage the fundamental causes of erectile dysfunction in patients affected by these medical conditions [51].

7.8. Hormonal Changes

Hormonal changes are also a crucial factor for erection. A few of the hormone which plays a major role in erection is listed below [52].

7.9. Testosterone

Testosterone (T) is a well-known essential hormone that plays a core or peripheral role in influencing male sexual response. As men age, their testosterone levels gradually decrease, which leads to erectile dysfunction.

7.10. Vascular Pathologies

Vascular factors mainly consist of two factors responsible for erectile dysfunction [53].

7.11. Hypertension

Another common cause of erectile dysfunction is hypertension or high blood pressure. Angiotensin II, endothelin 1, and aldosterone are pro-contractile substances released persistently and widely during hypertension. This imbalance between vasoconstrictors and vasodilators adversely affects vascular and erection structures [53].

7.12. Atherosclerosis

The deposition of plaque (fats) into the arteries is called Atherosclerosis. It may cause a higher deficit in blood flow which steers to erectile dysfunction [54].

7.13. Medical need

Despite significant advancements in the therapeutic intervention of erectile dysfunction (ED), certain patient groups show poorer response rates to currently available therapies. These populations include individuals with diabetes, post-prostatectomy patients, those with hypogonadism, and individuals with veno-occlusive dysfunction. In diabetes, ED arises from endothelial dysfunction, reduced enzymatic function of endothelial nitric oxide synthase, heightened contractile sensitivity, and impaired nitrergic nerve signaling [55]. Such disruptions occur before the target site of phosphodiesterase type 5 inhibitors, limiting their efficacy. Post-prostatectomy, damage to the neurovascular bundle impairs proper molecular signaling involved in smooth muscle relaxation, leading to hypoxia, tissue fibrosis, and programmed cell death [56]. Hypogonadism patients require testosterone replacement therapy as testosterone regulates nitric oxide synthase and PDE5 expression, which is important for erectile function [57]. Veno-occlusive dysfunction, characterized by structural abnormalities, presents challenges for pharmacologic therapy [58].

7.14. Related Disease States

Although PDE-5 inhibitors have proven effective, many patients, particularly those with chronic conditions like diabetes mellitus (DM) and cardiovascular disease (CVD), still do not respond to this therapy due to impaired NO release. Exploring these disease states can offer valuable insights into the underlying causes of refractory erectile dysfunction (ED).

7.15. Cardiovascular Disease

Cardiovascular diseases (CVD) and erectile dysfunction (ED) share reduced vascular endothelial function and reduced nitric oxide bioavailability, leading to a high coexistence. Diabetes mellitus, smoking, hypercholesterolemia, and high blood pressure, related risk factors for both conditions, contribute to their coprevalence[59]. ED has been substantially linked to (CVD), and (CVD) related deaths, but its predictive value for CVD is not superior to traditional risk factors [60]. PDE-5 inhibitors are contra-indicated to patients prescribed with nitrates.[61]. In hypertension, arterial stenosis, apart from high blood pressure, is linked to the development of ED [62]. Hypertensive patients may experience endothelial changes in the penis before systemic vascular dysfunction, with oxidative damage playing a role [59]. Hypertension is correlated with impaired endothelium-mediated smooth muscle relaxation, potentially involving the synthesis of nitric oxide by endothelial nitric oxide synthase [63]. Animal studies have shown that ischemia/hypertension models result in nerve and smooth muscle alterations in the penis [64]. Given the association of endothelial dysfunction with various vascular diseases, ED serves as a warning sign for silent vascular disease [65].

7.16. Diabetes

The Massachusetts Male Aging Study (MMAS) discovered that diabetic men have a threefold higher risk of developing erectile dysfunction (ED) than non-diabetic men [66]. ED in diabetes is associated with peripheral vasculopathy, neuropathy, and chronic hyperglycemia-induced micro- and macrovasculopathy, including endothelial dysfunction. The risk factors for diabetic ED are hypertension, advanced age, retinopathy, diabetes duration, obesity, poor glycemic control, and hyperlipidemia[67].

7.17. Priapism

An erection lasting longer than 4 hrs without any sexual stimulation is referred to as priapism[68]. The sinusoidal endothelium and cavernosal smooth muscle cells are damaged as a result of prolonged erection caused due to ischemic and intermittent priapism [69]. In (SCD) patients, priapism is prevalent, where free hemoglobin oxidizes nitric oxide (NO), leading to hemolytic endothelial dysfunction [70]. Various vasoactive signaling molecules like Rho-kinase, nitric oxide, adenosine, etc., are affected, thus resulting in ED. Additionally, priapism can be caused by long-acting erectile function-promoting agents [68].

7.18. Drug-Induced erectile dysfunction (ED)

A fraction of newly reported cases, encompassing approximately 25%, diagnosed as erectile dysfunction (ED) cases may be attributed to the side effects of certain drugs [71]. Antihypertensive medications, particularly thiazide diuretics, are reported to have a higher incidence of ED than other antihypertensive agents. The exact mechanism is unclear, but it is speculated that diuretics may interfere with smooth muscle relaxation [72]. Calcium channel antagonists and ACE

inhibitors have fewer negative effects on sexual function than diuretics, centrally acting agents, and beta-blockers [73]. Spironolactone, an aldosterone antagonist, can cause ED through an antiandrogenic mechanism [74]. Due to the antiadrenergic effects of B-blocking agents like atenolol and propranolol, slight psychological depression has been linked to ED [75]. ED can be managed by decreasing the adrenergic output caused by centrally acting antihypertensives such as methyldopa[76-79]. However, ED has been observed as a common side effect associated with the use of anti-depressants.[62]. Increased prolactin levels associated with the use of H2-antagonist cimetidine and phenothiazine antipsychotics (chlorpromazine and thioridazine) have also been linked to ED [80-82].

8. EMERGING TREATMENT FOR ERECTILE DYSFUNCTION

8.1. Melanotan II and bremelanotide: MCR agonists

Researchers have investigated the potential of melanocortin receptor (MCR) agonists, including melanotan II and bremelanotide, for treating erectile dysfunction (ED). Melanotan II, originally studied for tanning purposes, exhibited pro-erectile effects in a Phase I trial. Subsequent administering Melanotan II to men with erectile dysfunction (ED) produced substantial outcomes. Penile erections even without sexual stimulation, although notable side effects such as severe nausea and yawning were observed [83]. In contrast, intranasal administration of bremelanotide showed clinically significant erectile responses compared to placebo, with an onset of erection within approximately 30 minutes [84]. A Phase IIb trial of bremelanotide in patients with diabetes-induced ED found that the International Index of Erectile Function-Erectile Function domain scores improved significantly to [85]. In patients who had failed treatment with PDE5 inhibitors, bremelanotide demonstrated superior IIEF scores and overall sexual satisfaction [86]. Intranasal bremelanotide was discontinued due to side effects, and researchers are now focused on developing a subcutaneous form to enhance control and reduce adverse events. Phase III trials using the subcutaneous formulation are expected to be conducted [87].

8.2. ABT-724 and ABT-670: Dopamine agonists.

Selective dopamine D4 receptor agonists, ABT-724 and ABT-670, demonstrated promise in preclinical trials. ABT-724 induced erections in rats without typical dopamine-related side effects [88]. Combining ABT-724 with sildenafil synergistically enhanced erections, suggesting potential benefits for severe erectile dysfunction [89]. However, ABT-724 has no ongoing clinical trials due to strategic misalignment. ABT-670, another D4-selective agonist, exhibited superior oral bioavailability and comparable efficacy to ABT-724. Unfortunately, both ABT-724 and 670 were discontinued during Phase I and II regarding the expansion in their respective paths. [90].

8.3. Clavulanic acid (Zoraxel)

Clavulanic acid has exhibited the ability to promote erections. In nonhuman primate studies, it demonstrated an increase in sexual arousal and penile erections by enhancing serotonin and dopamine activity [91]. Administering different clavulanic acid doses over 14 days resulted in increased ejaculations, confirming its pro-sexual effects. A Phase IIa study in erectile dysfunction patients demonstrated dose-dependent improvements in Sexual performance and general quality of life. However, a planned Phase IIb trial in 2010 was subsequently suspended [92].

9. PERIPHERALLY ACTING AGENTS

9.1. BAY 60-4552: sGC stimulator/activator.

The effectiveness of PDE5 inhibitors (PDE5-Is) in treating erectile dysfunction (ED) relies on cGMP production, which is dependent on NO-mediated activation of sGC. However, patients with impaired NO release, such as people with diabetes or post-prostatectomy individuals, may exhibit a limited response to PDE5-Is. Directly stimulating sGC, independent of NO availability, is a promising approach. The native form of sGC is galvanized by Heme-dependent stimulators like BAY 63-2521 and 60-4552 to synergize with nitric oxide, while heme-independent activators (BAY 58-2667) activate the pathologic form induced by oxidative stress [92]. Animal and in vivo studies have shown improved erectile function with BAY 60-4552 alone or combined with a PDE5-I[93, 94]. However, a Phase II study comparing BAY 60-4552 (1 mg) and vardenafil (10 mg) combination to vardenafil alone did not demonstrate the superiority of the combination treatment [95].

9.2. Rho-kinase inhibitors: fasudil, SAR407899

Rho-kinase inhibitors have shown promise as potential treatments for erectile dysfunction in diabetic patients. The reduced NO production causing enhanced smooth muscle contractility is associated with neuronal and diabetes-related endothelial dysfunction. The upregulation of the ROCK pathway exacerbates this contraction. Fasudil and Y-27632, tested in diabetic rat models, restored relaxation responses and improved erectile function [96]. SAR407899, a potent Rho-kinase inhibitor, demonstrated efficacy in relaxing corpora cavernosa in human and animal studies, particularly in diabetic animals [97, 98]. However, a Phase II clinical trial with SAR407899 showed limited efficacy in increasing penile rigidity compared to placebo and sildenafil. Development of SAR407899 has been discontinued because of less efficiency [99].

9.3. Maxi-K channel activators: NS-11021

The maxi-K channel is a vital negative feedback system that links increased intracellular calcium levels to potassium currents, resulting in outward hyperpolarization. Researchers are studying compounds that activate these channels and increase erectile function. NS1619, an early activator, showed therapeutic potential for smooth muscle disorders, including erectile dysfunction (ED), but its clinical use was limited due to low potency and adverse effects [100]. The development of NS11021, a more selective and potent activator, demonstrated its ability to induce relaxation in penile arteries and corpus cavernosum, producing erectile responses comparable to sildenafil [101,102]. Andolast, currently in Phase III clinical trials, is the sole maxi-K channel-targeting drug candidate under development for mild/moderate asthma. At the same time, other studies explore its studies in bladder function and myocardial ischemia [100].

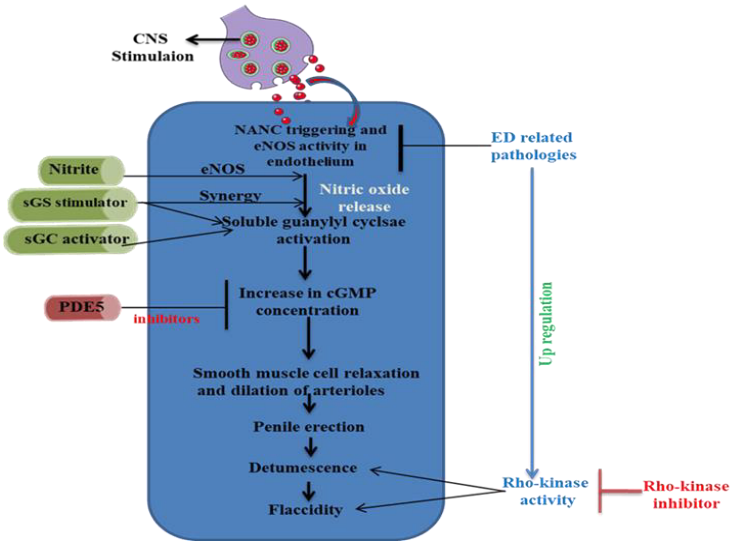

Fig. 6:- Pathway for control of penile erection [103]

The control of penile erection and detumescence involves complex pathways. Stimulation from higher brain centers triggers increased cholinergic and non-adrenergic non-cholinergic activity while reducing sympathetic activity in penile nerves. This increases nitric oxide release from the endothelium and NANC nerve terminals. NO binds to soluble guanylate cyclase, boosting cyclic guanosine monophosphate (cGMP) synthesis. cGMP-dependent protein kinase activates potassium channels, reduces intracellular calcium levels, and relaxes smooth muscle cells. This promotes the flow of blood into the penis, causing an erection. Detumescence occurs when vasoconstrictors are released, and cGMP is broken down by phosphodiesterase 5. Novel treatment targets include Rho-kinase inhibitors, sodium nitrite, and sGC stimulators/activators, which enhance NO-mediated effects and counteract erectile dysfunction.

9.4. Disease conditions

Erectile dysfunction can be prompted by some disease conditions, for exa -mple, cardiovascular disease, hyperlipidemia, diabetes, chronic kidney disease, and reproductive cancer [104].

9.5. Diagnosis of Erectile dysfunction

ED can be diagnosed by several methods, (Table- 2.)

Table- 2: Diagnostic methods of erectile dysfunction

Sr. no.	Diagnostic method name	Procedure	References
1.	Physical examination	Diagnosing erectile dysfunction requires a thorough physical examination that evaluates various aspects of genital and prostate health. Medical professionals typically measure blood pressure, assess peripheral pulse, and examine the size and texture of the testicles. They also evaluate penile sensation and look for abnormalities in the penis or surrounding areas, such as Peyronie's plaque or hypospadias.	105
2.	Sexual history	Clinician asks some questions from patients about their sexual history to diagnose erectile dysfunction, such as "How's your sex life?". A patient should respond to this kind of question with a loud, concise, and straightforward "Everything is fine." Any other reaction or a pause in communication should raise suspicions that the patient may have an ED.	106
3.	Medical history	Medical history should obtain about any preceding surgical procedures or several medical disorders.	107
4.	Laboratory testing	To confirm erectile dysfunction, fasting glucose level, fasting lipid profile, prostate-specific antigen test, and total testosterone level are performed.	108
5.	Screening of ED	IIEF-5 questionnaires are utilized to screen the ED.	109
6	Apomorphine test	Streptozotocin is injected intraperitoneally to cause type I diabetes; after that apomorphine test is used to measure erectile function.	110
7.	NPTR test	The test for nocturnal penile tumescence and rigidity is an effective technique for diagnosing and treating erectile dysfunction. It assesses erectile function and is a crucial tool for separating organic from psychogenic causes of impotence.	108
8.	Biothesiometry test	A method known as biothesiometry is used to assess the sensory power of the neurons in the penis. By vibrating the glans and both sides of the penile shaft using an electromagnetic test probe, ask the patient to describe when he feels the vibration.	111
9.	Color duplex Doppler	The gold standard for identifying males with vascular ED is the color duplex	112

	ultrasound test	Doppler ultrasonography. Color Doppler imaging is performed for both cavernous arteries after intravenously delivering a vasoactive drug (such as 10 g of alprostadil). PSV (Peak systolic velocity) < 25 cm/s is used to diagnose arterial insufficiency, while PSV > 35 cm/s indicates adequate arterial function.	
10.	CTA	CTA is a useful diagnostic tool for detecting peripheral arterial lesions with the help of specific dye.	[113]
11.	Non-coding RNA as a biomarker	A biomarker is used to investigate erectile dysfunction caused by diabetes mellitus.	[114]
12.	Psychological assessment	Men with ED may benefit from psychological evaluation to learn more about the influence of their relationships, cultural and religious factors, depression, and other psychological problems.	[115]
13.	Neurophysiology test/ Electromyography (EMG)	Neurophysiology test examines the peripheral nerves by stimulating the nerves with safe tiny electrical pulses, like that of static shocks, and recording the response.	[116]
14.	Androgen symptoms of age (AMS)	AMS scale is widely used for screening men suspected of erectile dysfunction.	[117]
15.	Male copulatory function scale (MCF)	It is a scale for the total quantification of male copulative function that facilitates diagnosing and observing MCF abnormalities and controlling MCF amendment. The scale is based on normal values provided by statistical data on the sexual activity of males and its age-related changes.	[117]

Table- 2. Erectile dysfunction (ED) is a common problem that affects many men worldwide. Diagnostic methods are available to identify the underlying cause of ED and guide treatment. These include physical examination, sexual history, medical history, laboratory testing, screening questionnaires, and various specialized tests such as the apomorphine test, NPTR test, biothesiometry test, and color duplex Doppler ultrasound. Psychological evaluation and androgen symptoms of age and male copulatory function scales can also aid in diagnosing ED. Clinicians should consider utilizing these diagnostic methods comprehensively to diagnose and manage ED [118] accurately.

9.6. Management of ED

(ED) is a predominant disorder that makes it difficult for men to achieve or maintain an erection adequate for sexual intercourse. Physical, psychological, and lifestyle issues can cause ED for various reasons. The management of ED depends on the underlying cause of the condition (Fig. 7). But the following is some of the latest knowledge on the management of ED [119].

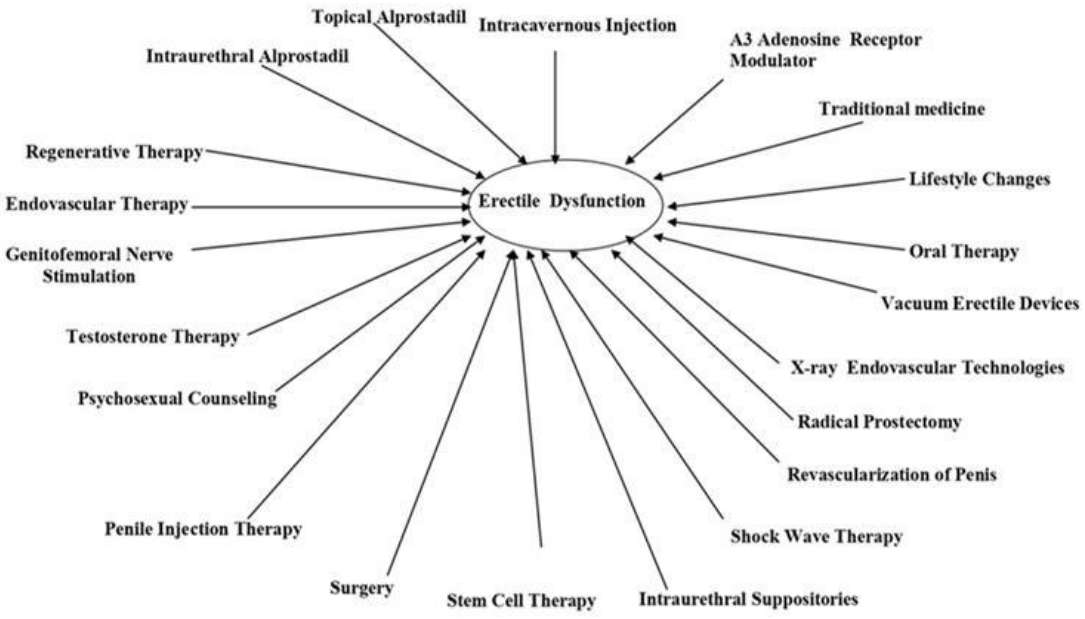

Fig. 7:- Management of Erectile Dysfunction [118].

A detailed summary of different approaches for managing erectile dysfunction. It's great that many options are available for patients, ranging from traditional medicine to high-tech procedures such as X-ray endovascular technologies. It's also interesting that lifestyle changes, such as reducing sedentary behavior and controlling calorie intake, may improve sexual performance. Overall, the field of erectile dysfunction management seems to be quite diverse and rapidly advancing.

9.7. Intracavernous injection

Bieri et al., (2020) use the Magellan devices two 12 in. to carry out the clinical study of intracavernous injection as an extraction of caverstem 1.0, a low dose of 3 ml, or a high dose of 6 ml of sterile bone marrow concentrate. They injected bone marrow concentration of about 1.5 or 3.0 ml with 25 gauze needles [105].

9.8. A3 adenosine receptor modulator

Itzhak et al., (2022) found that an A3 adenosine receptor allosteric modulator rectifies the binding properties of endogenous adenosine to the receptor. Attaching to its receptor and activating a pathway that increases intracavernosal pressure, arterial blood flow, and adenosine play a crucial role in erection [120].

9.9. Traditional medicine

Yang et al., (2022) used traditional hirudinto treat diabetic ED. Hirudin is an active ingredient obtained from the leech. A novel strategy is intended for them to find out possible destinations based on the investigating tools of traditional Chinese medicine (TCM), and they found that MPO (myeloperoxidase) is a promising target of hirudin. Hirudin interacts with myeloperoxidase directly and blocks its function, further reducing the amount of oxidized low-density lipoprotein in serum. According to their findings, hirudin can help with the symptoms of diabetic erectile dysfunction [121]. Sun et al., (2022) also used the traditional Chinese medicine Paeonol (pae) to treat diabetic erectile dysfunction [122].

Table- 3:Some herbal products used in the treatment of ED are listed

Sr.no.	Medicinal Plants	Traditional use	Potential benefits	References
1	*Panax ginseng*	Traditional Chinese medicine	It may improve sexual function and increase testosterone levels in men.	[123]
2	Horny goat weed (Barrenwort)	Traditional Chinese medicine	It can potentially enhance blood circulation to the genital area and enhance sexual performance.	[124]
3	Yohimbe obtain from *(Corynanthe yohimbe)*	Traditional African medicine	This may enhance penile blood flow and ameliorate sexual function.	[125]
4	*Tribulus Terrestris*	Traditional medicine	It could potentially boost testosterone levels and enhance sexual function.	[126]
5	*Ginkgo biloba*	Traditional Chinese medicine	It may improve blood flow, sexual function, and libido.	[127]

Table- 3. Presents a selection of herbal products commonly used in traditional medicine for sexual health. Panax ginseng, a traditional Chinese medicine, may enhance sexual function and increase testosterone levels in men. Horny goat weed can improve blood circulation to the genital area and enhance sexual performance. Yohimbe, derived from traditional African medicine, may enhance penile blood flow and improve sexual function. Tribulus Terrestris, a traditional medicinal herb, shows promise in boosting testosterone levels and enhancing sexual function. Ginkgo biloba, another traditional Chinese medicine, may improve blood flow, sexual function, and libido.

9.10. Lifestyle changes

According to Defeudis et al., (2022), sedentary lifestyles, overweight/obesity, and higher calorie intake have all been linked to the emergence of diabetes mellitus erectile dysfunction. And altering one's way of life might enhance sexual performance [128].

9.11. Oral therapy

Salvio et al., (2022) utilized many therapies to manage erectile dysfunction. They introduced oral therapy as a Phosphodiesterase 5 inhibitor class of drugs like (SIL), (VAR), (TAD), and Avanafil. These medications prevent the vessel's smooth muscle cells from producing the enzyme phosphodiesterase-5 (PDE-5). PDE-5 inhibitor stops PDE-5 from degrading to the cGMP by blocking this enzyme. Protein kinase G may be activated by GMP, which will relax the vascular smooth muscle [129]. Some of the marketed products, active ingredients, and manufacturers are listed in Table - 4.

Table- 4: List of marketed products, active ingredients, and manufacturers.

Sr. no.	Marketed product	Active ingredient	Manufacturer
1	Manforce Tablet	Sildenafil	Mankind Pharmaceutical Ltd.
2	Esylnafil Tablet	Sildenafil	Avighana Medicare Pvt. Ltd.
3	Vigore 100 Tablet	Sildenafil citrate	German Remedies Ltd.
4	Varimax Tablet	Vardenafil	Macleods Pharmaceuticals
5	Tadaflo 5 Tablet	Tadalafil	Cipla Limited
6	Tadact 10 Tablet	Tadalafil	IPCA laboratories
7	Tazzale 5 Tablet	Tadalafil	Dr. Reddy's Laboratories Ltd.
8	Avanair 100 Tablet	Avanafil	Cipla Ltd.
9	Avanext 100 Tablet	Avanafil	Zydus Cadila Healthcare Ltd.

Table- 4. Showcases a range of commonly marketed erectile dysfunction (ED) medications, along with their respective active ingredients and manufacturers. Manforce Tablet by Mankind Pharmaceutical Ltd. contains Sildenafil. Esylnafil Tablet by Avighana Medicare Pvt. Ltd. also contains Sildenafil. Vigore 100 Tablet by German Remedies Ltd. contains Sildenafil citrate. Varimax Tablet by Macleods Pharmaceuticals contains Vardenafil. Tadaflo 5 Tablet by Cipla Limited contains Tadalafil. Tadact 10 Tablet by IPCA laboratories also contains Tadalafil. Tazzale 5 Tablet by Dr. Reddy's Laboratories Ltd. contains Tadalafil. Avanair 100 Tablet by Cipla Ltd. contains Avanafil. Avanext, 100 Tablet by Zydus Cadila Healthcare Ltd., also contains Avanafil.

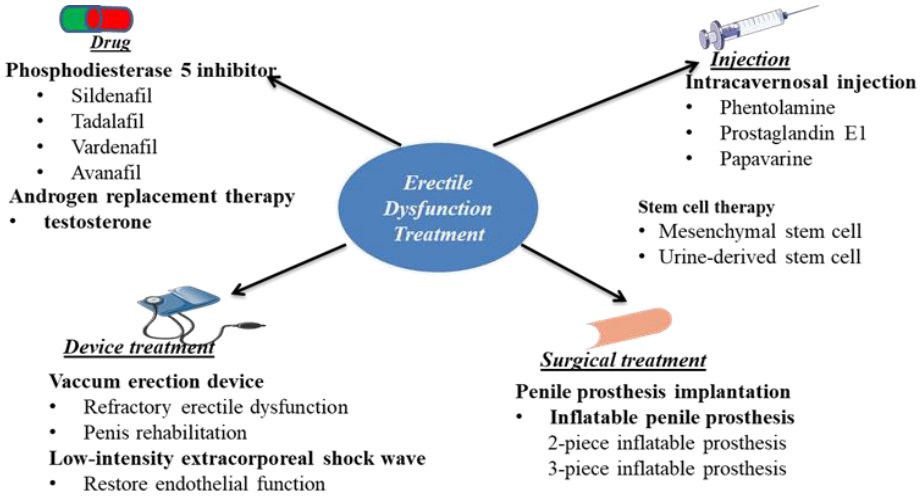

Fig. 8:- Summary diagram of the treatment of erectile dysfunction

9.12. Vacuum erectile devices

Sultana et al., (2022) highlighted the use of the vacuum erection device (VED) in managing erectile dysfunction. The VED can be used before the insertion of a penile prosthesis to increase the stretched penile length and facilitate implant insertion. This device is the most commonly utilized therapy for male sexual function among all approved methods. The VED has been used for almost 150 years for treating ED, and it was approved by the U.S. Food and Drug Administration in 1982. The American Urological Association (AUA) recognized it as a standard of care in 1996 [130]. Vacuum erectile devices consist of a cylinder made of clear plastic and a vacuum device that can be operated manually or by battery. To keep an erection for penetration while using the VED, constriction rings may be employed. With a VED, a satisfactory erection can be obtained in 30 seconds to 7 minutes [131].

9.13. X-ray endovascular technologies

Popov et al., (2020) provided reliable data on the improvement in the quality of the erectile component of the copulatory cycle in the first 3 months after x-ray endovascular vein occlusion of the prostatic plexus [117].

9.14. Radical prostatectomy

Rho et al., (2022) described in their articles the ED treatment post radical prostatectomy followed by phosphodiesterase 5 inhibitor for the management of erectile dysfunction. A radical prostatectomy involves removing the prostate gland and its surrounding tissues. The seminal vesicles and a few adjacent lymph nodes are typically included in the radical prostatectomy [132].

9.15. Surgery

According to Anderson et al., (2022), microvascular arterial bypass surgery can be used to revascularize the penile in cases of arterial insufficiency. The dorsal penile artery is frequently revascularized and anastomosed with the inferior epigastric artery. Although anastomosis to the dorsal artery is desired, anastomosis to the deep dorsal vein can also revascularize the inferior epigastric artery. The AUA gives a grade C recommendation for penile arterial reconstruction. To keep blood in the corpora cavernosa during erection, penile venous surgery seeks to obstruct venous drainage [133].

9.16. Shockwave therapy

According to Yao et al., (2022), a low-intensity extracorporeal shockwave has been widely utilized to treat erectile dysfunction because it stimulates the function of angiogenesis-related factors like vascular endothelial growth factors [134]. Shockwave therapy, also known as extracorporeal shockwave therapy (ESWT), was initially used for clinical purposes to treat urologic problems in 1982. Gruenwald et al., (2013) also used low- intensity of extracorporeal shockwave for the management of erectile dysfunction. They applied shockwave therapy on five distinct sites of the penis by exposing 300 SWs (intensity of 0.09 ml/mm^2), two at the crural level and three along the penile shaft. The treatment plan included two weekly therapy sessions for three weeks, a three-week break of no therapy, and another three-week stint of weekly therapy [135].

9.17. Intraurethral suppositories

Hew and Gerriets et al., (2021) used an Intraurethral suppository of prostaglandin E1 (PGE1) via the intraurethral route. The suppository must be inserted immediately after urination. The applicator stem will get inserted into the urethra to deposit the medicinal suppository [136].

9.18. Stem cell therapy

Manfredi et al., (2022) reported in their articles about stem cell therapy utilized for managing sexual dysfunction. It is a form of regenerative medicine designed to repair the damaged cells within the erectile system [137].

9.19. Penile injection therapy

Islam et al., (2022) mentioned in their article about penile injection, such as platelet-rich plasma injection used in ED management [138].

9.20. Psychosexual counseling

As Stainer et al., (2022) reported in their article, psychosexual counseling has long been an efficient part of the management strategy for treating ED. It can aid in improving

the result of penile rehabilitation of some managements and the compliance to stay on therapy [139].

9.21. Testosterone therapy

According to Corona and Maggi (2022), testosterone is key in controlling male sexual response, functioning centrally or peripherally. To treat erectile dysfunction, testosterone replacement therapy (TRT) has been employed [140].

9.22. Genitofemoral nerve stimulation

Dong et al., (2021) investigated that erectile function was saved by stimulation of the genitofemoral nerve stimulation to the pelvic nerve preserved erectile function [141].

9.23. Endovascular therapy

Wang et al., (2022) studied endovascular therapy for treating erectile dysfunction associated with hypertension by targeting arterial insufficiency [142].

9.24. Regenerative therapy

Kim et al., (2021) reported in their articles about regenerative therapy as an adipose-derived cell for managing sexual dysfunction [143].

9.25. Intraurethral alprostadil

Moncada et al., (2018) described in their article a combination therapy along with intraurethral alprostadil for the management of erectile dysfunction [144].

9.26. Topical alprostadil

Hamzehnejadi et al., (2022) mentioned in their articles about topical alprostadil cream, which was used for sexual dysfunction management [145].

9.27. Use of nanotechnology in erectile dysfunction

Nanotechnology-based vehicles show great potential for improving erectile function in individuals with ED. These vehicles can transfer beneficial substances like proteins and stem cells to the penis, which have been identified as promising agents for enhancing erectile function. Nanotechnology-based vehicles can amplify the effects of growth factors and other helpful agents by providing better release, penetration, bioavailability, and targeted administration. Injectable gels can prevent changes in penis morphology after prostate surgery, while hydrogels can promote regeneration and neuroprotection. Overall, these innovative vehicles hold tremendous promise for advancing ED research and offering effective translational therapy for patients with ED. Topical drug delivery for on-demand erectile function and drug encapsulation for ED treatment are the four main applications of nanotechnology for ED treatment.Animal studies conducted in vitro and in vivo have produced promising results, demonstrating significant and measurable improvements in erectile function without any noticeable immune response. However, further toxicology and pharmacology studies are required to ensure that the breakdown and degradation of nanomaterials in small and large animal models do not have any adverse effects. Such studies are critical for future applications and translation of this technology to humans [146-148]. The toxicity of the nano-materials being studied for ED research still needs to be understood. The experiments discussed in this review are cutting-edge regarding the delivery of biological materials, but pre-clinical toxicity testing has yet to be possible. This is a crucial next step for several of the nanomaterials shown. The hardest obstacle to clinical study and application will be the requirement of FDA approval. The process of obtaining FDA approval is drawn out and expensive, and most scientists working in the field need more guidance on how to make this move.

10. CONCLUSION

Erectile or sexual dysfunction is a familiar disease related to diminished personal satisfaction for men and their accomplices. Multiple physical, psychological, neurological, hormonal, and vascular pathogenesis factors cause erectile dysfunction. The initial symptoms of erectile dysfunction are endothelial dysfunction. ED can be diagnosed by several methods such as physical examination, laboratory testing, IIEF-5 questionnaires, and color duplex Doppler ultrasound test. Erectile dysfunction can be treated alone, through combination or psychological therapy. All these therapies are effective in treating or restoring sexual function. Overall, there is substantial agreement regarding the handling of ED. There are a few inconsistencies in chosen guidelines for ED.

11. ABBREVIATION

MCG -Medicated Chewing gum
PVP - Polyvinylpyrrolidone
GB - Gum base
VAR – Vardenafil

12. AUTHORS' CONTRIBUTION STATEMENT

Ram Ajay Gupta made substantial contributions to the initial draft of the manuscripts and played a crucial role in developing the Figure and Tables. Aditya Shiven played a significant role in the conceptualization and design of the manuscript and made substantial contributions to the editing process.

13. CONFLICT OF INTEREST

Conflict of interest declared none.

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