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REVIEW ARTICLE

The Phosphodiasterase 5-Inhibitors (PDE-5i) for Erectile Dysfunction (ED): A Therapeutic Challenge For Psychiatrists

Chong Siew Koon[1], Hatta Sidi[1,*], Jaya Kumar[2], Ong Wan Xi[3], Srijit Das[4], Muhammad Hizri Hatta[5] and Cesar Alfonso[6]

[1]Department of Psychiatry, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; [2]Department of Physiology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; [3]Hospital Bahagia Ulu Kinta, 31300 Tanjung Rambutan, Perak, Kelantan, Malaysia; [4]Department of Anatomy, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; [5]Zwirki I Wiguri 62, Medical University of Warsaw, Poland; [6]Department of Psychiatry, Columbia University Medical Center, 1051 Riverside Drive New York, New York 10032, USA

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Abstract: Erectile function (EF) is a prerequisite for satisfactory sexual intercourse (SI) and central to male sexual functioning. Satisfactory SI eventually initiates orgasm – a biopsychophysiological state of euphoria – leading to a sense of bliss, enjoyment and positive mental well being. For a psychiatrist, treating ED is self-propelled to harmonize these pleasurable experiences alongside with encouragement of physical wellness and sensuality. Hence, the role of PDE-5i is pivotal in this context and constitutes a therapeutic challenge. PDE-5i work *via* the dopaminergic-oxytocin-nitric oxide pathway by increasing the availability of endothelial's guanosine monophosphate (GMP), immediately causing relaxation of the penile smooth muscle and an erection. The PDE-5i, like sildenafil, vardenafil and tadalafil, are effective in the treatment of ED with some benefits/ flexibilities and disadvantages compared to other treatment modalities. Prescribed PDE-5i exclusively improve EF, fostering male's self-confidence and self-esteem. Treatment failures are associated with factors such as absent (or insufficient) sexual stimulation, psychosexual conflicts and the co-existence of medical disorders. Managing ED requires dealing with underlying medical diseases, addressing other co-morbid sexual dysfunctions like premature ejaculation (PE), and educating the patient on healthy life-styles. Furthermore, by dealing with interpersonal dynamics within the couple and embracing adequate lifestyles (managing stress and revising one's sexual scripts), PDE-5i treatment benefits may be enhanced. In this review, we propose a holistic conceptual framework approach for psychiatric management of patients with ED.

Keywords: Erectile dysfunction, PDE-5 inhibitor, psychiatric management of ED, body-mass index, hypertension, sexual fantasy.

1. INTRODUCTION

Erectile Dysfunction (ED) or erectile disorder, is a medical condition that is not uncommonly encountered in men, more notably especially after the age of 50, which greatly hampers sexual and marital satisfaction [1, 2]. Untreated ED may escalate with complexity causing marital conflict, mental distress and other psychosocial problems [1, 2]. ED usually is associated with endothelial abnormalities of the penile blood flow and underlying neurochemical dysregulation [4]. According to the DSM-5 [2], erectile disorder is "characterized by a recurrent inability to achieve or maintain an adequate erection during partnered sexual activities". ED occurs in up to 20% of men at some point throughout their lifetime [2], affecting approximately 150 million men globally. This figure is expected to increase to about 300 million by 2025 [3]. The main complaint commonly described by men with ED is the difficulty to attain and/- or sustain an erection during sexual performance. The diagnosis is made when the person remains significantly symptomatic for at least 6 months [2]. Other factors that must be taken into this consideration are to determine whether ED is generalized or situational; and if it is a mild, moderate or severe [2]. The prevalence rate of ED depends on the age of men in the sample assessed, and the methods used to identify ED [5]. Some of the factors contributing to erectile function [1-6] are outlined in Fig. (**1**).

Since the significantly serendipitous pharmacological synthesis and discovery in the 1980s of the ED-treatment properties of sildenafil, the first PDE-5i, almost a third of a century has passed [1, 3, 4]. With the passing of time, the

*Address correspondence to this author at the Department of Psychiatry, Faculty of Medicine, UniversitiKebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia; Tel: +603- +9145 6142; Fax: +603 – 9145 6681; E-mail: hattasidi@hotmail.com

role of psychiatrists in the treatment of ED in day to day clinical practice has evolved from a solitary endeavor to a link in a multidisciplinary practice. Accompanied by great challenges inherent to liaison work, psychiatrists have the capacity to fill the 'lacunae' among medical specialists. Even though ED is conceptualized as medical disorder [3, 4], general psychiatrists managing patients with ED recognize that psychotherapeutic work is part of the process, besides pure involvement in pharmacological practice. The benefits of "talk-therapy" as an adjunct treatment are based on ED-related psychological problems, *e.g.* relationship/ marital discord, and other ED-related psychological dimensions [5] like sexual conflicts. Psychiatrists work in alliances with general practitioners and urologists, and their place is eminent as psychological issues emerge and compound ED [5]. Hence, psychiatrists not only need to know how to inform and educate patients and perform psychotherapy, but also embrace a deep understanding of the neuro psychopharmacological basis of treatment with PDE-5i. *e.g.* clinical benefit, side-effects and drug-to-drug interactions.

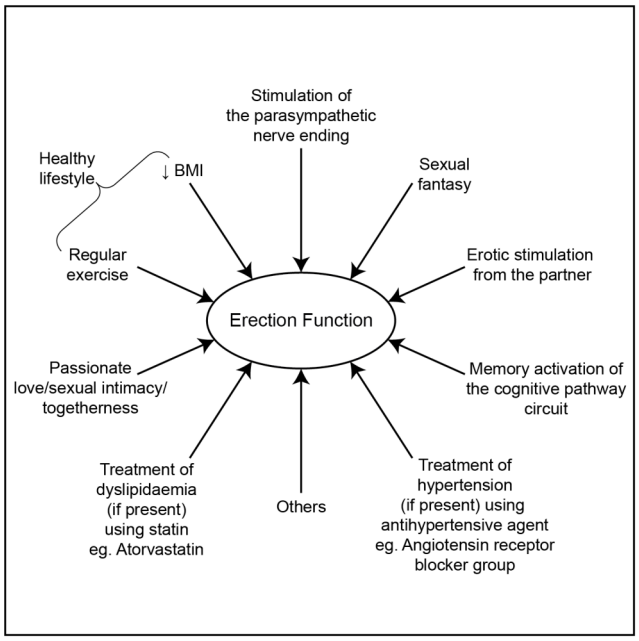

Fig. (1). Factors that determine erectile function (EF); BMI = Body-mass index.

2. THE PHOSDIASTERASE-5 ENZYME (PDE-5) AND PDE-5 INHIBITORS (PDE-5i)

PDE-5i mainly act on the phosphodiasterase-5 enzyme intracellularly in the endothelial penile smooth muscle [4]. There are different forms and subtypes of phosphodiesterase (PDE) identified, all with various functions [3, 4]. Our main interest in this context would be that of PDE-5, which has been proven to be essential for EF. PDE was found to be selectively inhibited in the body, including in the brain and other tissues, by a variety of drugs. The potential for selective PDE-5i as treatment agents was predicted as early as the 1970s [3, 4]. PDE-5 is responsible for the breakdown of cyclic guanosine monophosphate (cGMP), which in turn decreases the availability of nitric oxide (NO) in blood vessels [4-6]. This mechanism controls the degree of erection in men. However, in men suffering from ED, the presence of PDE-5 may hamper sexual performance. The discovery of this enzyme and the invention of drugs simulating its structural function has become the basis of state of the art pharmacological treatment of ED [4, 6].

Fig. (**2**) summarizes the biochemistry that underlies PDE-5 action as it is influenced by myriad factors [4, 6]. Stimuli such as visual, olfactory, tactile and auditory, sexual fantasy, or a combination of more than one of these, brings about the activation of memory-cognitive excitation of the hippocampus and the limbic system [4]. This in turn generates an impulse to the supraoptic (SO) and paraventricular (PV) nuclei that releases multiple chemicals essential to activate neuronal nitric oxide synthetase (nNOS) *via* dopaminergic projection fibres [4]. Neurochemicals and neuromodulators such as oxytocin, glutamate, dopamine, opiods, serotonin, γ-amino butyric acid (GABA) and endogenous opiods have been identified as important substances that act as inducing and inhibitory agents for NO release [4]. The nNOS produces NO within intracellular ambience of cells [4, 6], which participates in a 'miniature cycle of its own' as shown in the centre of Fig. (**2**) where it leads to changes *via* Event A and Event B. Event A comprises the conversion of guanosine monophosphate (GMP) to cGMP by a membrane-bound enzyme guanylate cyclase within penile arteriolar smooth muscle. Event A is activated by action of PDE-5. Indirectly, PDE-5 also controls the degree and duration of erection. Event B is the extension of A, where PDE-5i inhibits the degradation of cGMP. The availability of cGMP forms a significant physiological event [4, 6]. cGMP leads to relaxation of the endothelial smooth muscle of the corpus cavernous. Calcium ions are involved as a cofactor that aids in the catalyzation and maintenance of this conversion step [4]. These events cause a free flow of blood, culminating in a penile erection.

Emotional excitement and positive affects further enhance pleasure through rewarding brain centre receptors in the dopaminergic-mesolimbic area, and these experiences are subsequently encrypted in the hippocampus, which later may play an important role when the SO and PV nuclei system release more NO [4]. A rapid fall of sexual arousal then gradually removes stimulation of the associated region, and NO is inhibited [4]; bring to conclusion sexual activity. However, some men are unable to achieve erection for initiation of SI while others are able to attain minimal EF but fall short of sustaining erections. The role of PDE-5 in this case would be its action on Event A to Event B where inhibition of the PDE-5 enzyme increases availability of cGMP which in maintaining availability of NO, hence sustaining erections [4]. In other words, PDE-5i protects cGMP from degradation by cGMP-specific phosphodiesterase type 5 residing in the corpus cavernosum [4]. NO release in corpus cavernosum of the penis (cCP) binds to guanylase cyclase receptors resulting in inceased levels of cGMP, leading to smooth muscle relaxation and vasodilation in the intimal cushion of the arteries [4, 6]. This ultimately brings increased blood rush into the spongy tissue of penis, leading to erection [4, 6].

3. PDE-5i DRUGS

Sildenafil, vardenafil and tadalafil are well known PDE-5i licensed for treatment of ED. Equipped with the fact that PDE-5 degrades cGMP, the molecular structures of the men-

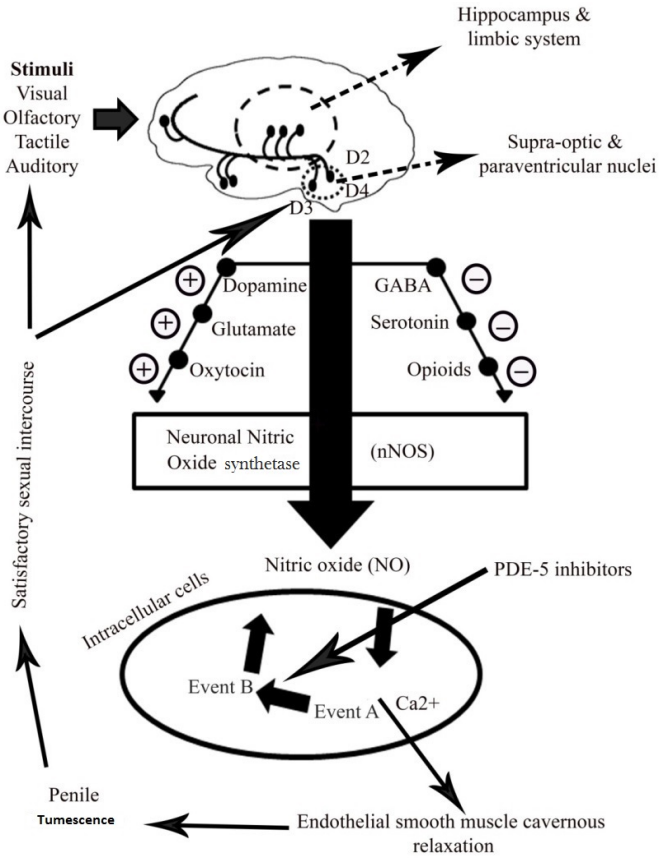

Fig. (2). Neuronal pathways, sexual stimuli and mode of action of phosdiasterase-5 inhibitors (PDE-5i). Event A = Stimulation of NO to convert GTP to cGMP *via* guanylyl cyclase, and; Event B = PDE-5 inhibitors prevent the breakdown of cGMP to GMP. Event B will cause accumulation of cGMP and lead to reduction in calcium ion (Ca^{2+}) and erections.

tioned drugs are modeled to replicate that of cGMP [4, 6]. This retains cGMP at higher levels, which relaxes smooth muscles, promotes penile blood flow, and enhances erectile function [6]. Pharmacological therapies are based on the fact that EF represents a balance between pro-erectile and anti-erectile mechanisms that control corporal smooth muscle tone. Sustained EF is achieved by either inducing smooth muscle relaxation through cell receptor agonist or direct activators of cCP tissue relaxant pathways (*e.g.* stimulating cGMP or cAMP synthesis) or disrupting the deactivation of smooth muscle relaxation pathways (*e.g.* inhibition of PDE-5 enzymes that inactivate cGMP or cAMP) [4, 6, 7]. Many studies have shown that the earlier generation of oral PDE-5 inhibitors, such as sildenafil, vardenafil, and tadalafil are effective and safe in more than 80% of unselected patients with ED, thus becoming the first-line pharmacologic therapy to improve EF [4, 6, 7]. What makes these highly effective drugs dangerous is that they interact with some other widely used substances such as nitrates, causing a decrease in blood pressure and at times hypotensive crises [4, 7]. It was argued that because ED is not a life-threatening condition and potential drug interactions can be lethal [4, 6], PDE-5i should not be casually approached as recreational or 'lifestyle enhancing drugs'.

4. SILDENAFIL - THE 'EARLIEST'

Sildenafil was the first PDE-5i approved by the U.S. Food and Drug Administration in 1998 for treatment of ED based on its efficacy and safety profiles in randomised clinical trials [7]. Other oral PDE5i, including tadalafil and vardenafil, have also been approved since then for treatment of ED [4]. Sildenafil is well absorbed orally; with an optimal timing of administration 30 minutes prior to the intended SI. Effects of sildenafil usually last between 15-70 minutes, but in some subjects for several hours. Commonly encountered side effects of sildenafil included headache, flushing, indigestion or epigastric discomfort, nasal congestion and "flu-like" symptoms, blurred vision, difficulty with visual accomodation leading to decreased visual acuity, photophobia and impaired night-vision [8, 9] (Fig. **3**). In October 2007, the FDA announced a warning with regards of visual impairment in association with all 3 PDE-5 i drugs, although the realtive incidence of serious visual impairment is relatively low [10-12]. Sildenafil, as with other PDE-5 inhibitors, is metabolised *via* the cytochrome P450 pathway in the liver, utilising CYP3A4 as a major pathway and CYP2D6 as a secondary pathway [13, 14].

5. TADALAFIL - THE 'LONGEST'

Tadalafil is a more specific PDE-5 inhibitor with a shorter onset and longer duration of action than sildenafil. Treatment with tadalafil leads to successful SI, and sexual attempts can occur up to 36 hours after first dose *via* oral ingestion [4, 6, 7, 10-12]. Headache and dyspepsia are the most common side effects (Fig. **3**), but with insignificant

visual side-effects [4, 10-12]. It is also used worldwide for on demand dosing in the treatment of ED and also for a variety of other medical illnesses such as benign prostate hypertrophy [15]. Tadalafil has been a main competitor of sildenafil in terms of the treatment of choice of ED [4, 10-12]. Some patients experience fewer side effects with tadalafil, especially those associated with blurring of vision whilst some prefer the fact that its therapeutic effect lasts longer. However, longer duration of action can be a disadvantage in certain conditions where respondents report sustained erections for periods longer than desired, even when simply taking bath with water running through to their inguinal area. Erections may even occur when the penis is accidently rubbed or touched [4, 6, 7, 10-12]. Like sildenafil or vardenafil, tadalafil is used for patients with ED, on an as when required basis (Table **1**). Unlike others, though, tadalafil offers a once per day dosing in view of its sustained effect, an advantage which many patinets find favourable in terms of dosing convenience (Table **1**). Tadalafil negatively interacts with alcohol, and patinets should be warned that erven casual consumption of alcohol may act synergistically causing dangerous hypotension.

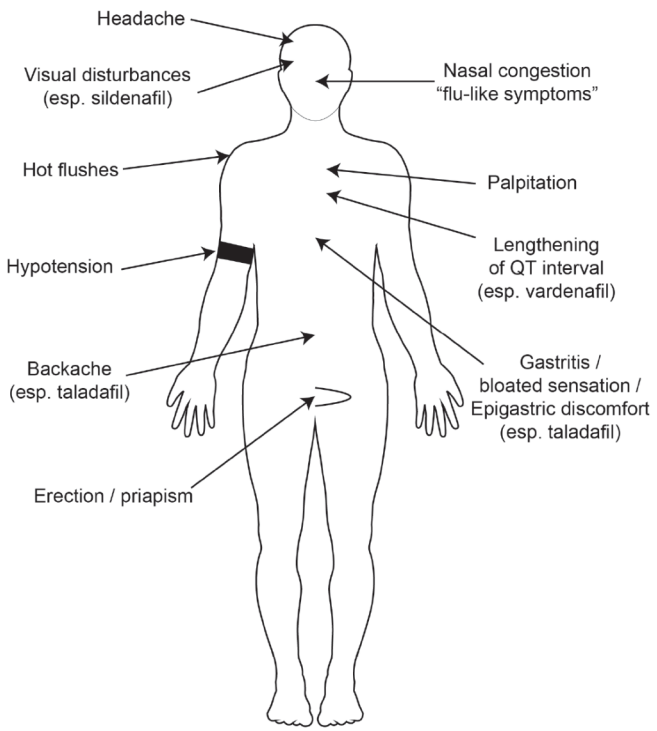

Fig. (3). The side-effects of PDE-5-Inhibitors.

Most commonly encountered side effects of tadalafil are stomach or epigastric discomfort [15]. Some men reported frequent bloating sensation in the epigastrium, post ingestion with acid reflux whilst others complained of backache and even 'flu-like symptoms' [4, 10-12] (Fig. **3**). These side effects are usually due to the vasodilation action of PDE-5i. However, these symptoms are usually minimal and disappear after few hours. Muscular backache may occur 12-24 hours post ingestion and resolves after 48 hours. Headaches and backache may improve with simple analgesic prescription such as oral paracetamol.

Although all 3 drugs discussed work *via* PDE-5 inhibition, tadalafil's distinctive pharmacological property would be of its prolonged half life (**t½**) of 17.5-hour vis-a-vis sildenafil and vardenafil [4, 6]. Besides the known PDE-5 inhibition, tadalafil also acts on PDE-11 more than both sildenafil or vardenafil. PDE-11 receptor sites are found in skeletal muscle, prostate, liver, kidney, pituitary and testes [4, 6, 10-13]. The significance of such action is still unknown.

6. VARDENAFIL - THE 'STRONGEST'

Vardenafil has a pharmacokinetic property which is nearly similar to that of sildenafil. It is well absorbed orally and metabolized *via* hepatic CYP3A4. It's **t½** is also an approximate to sildenafil; in the range of 4-5 hours. Vardenafil, as with all PDE5i, should not be used by men taking nitrate medications, because these combinations might be leading to a potentially life-threatening hypotensive danger.

In additional to the context of cardiological side-effects, vardenafil caused prolongation of the QT interval. Therefore, it should not be taken by men prescribed with other medications that affect the QT interval such as amiodarone, an antiarrhythmic drug used to treat ventricular tachycardia (or ventricular fibrillation) [16]. Vardenafil is available in 2.5 mg, 5 mg, 10 mg, and 20 mg doses. It is a potent PDE-5i, with the normal starting dose is 10mg with dose equivalent to 50 mg of sildenafil, achieving penile tumescence comparable or even surpassing it's counterparts [17]. Vardenafil should be taken 1 to 2 hours prior to SI, with a maximum dose frequency of once per day [18].

7. PDE-5i SIDE EFFECTS, THERAPEUTIC EFFECTS AND GENERAL CONCERNS

A more severe side effect of all PDE-5i is priapism, which is a sustained, painful erection that at times requires emergency management and if untreated may lead to fibrosis and impotence (Fig. **3**). Some patients taking nitrates or antihypertensive agents like β-blockers may experience acute syncopal episodes [4, 6, 7, 10-13].

According to the research available to date, all three PDE-5 inhibitors are effective agents to treat ED [19-21]. For example, the treatment with vardenafil in a dose of 20 mg produced an improvement in the EF ability to reach an erection in 80 % of ED patients [22]. In a comparable study of sildenafil (100 mg dose), more than 80% of patients with ED were successfully treated [22]. Intervention with tadalafil 25 mg produced an improvement in the ability to achieve a good EF in 81% of ED patients [4, 10-13, 19-21]. If PDE-5i efficacy is compared to placebo, the differences between sildenafil, vardenafil and tadalafil respectively with placebo are even clearer, where the former is significantly improves EF than the latter. In comparison with placebo, intake of oral tablet of 100 mg sildenafil leads to significant improvement EF; similarly with 20 mg vardenafil, and treatment with 10 mg vardenafil [6, 7, 10-13, 19-21].

The expected and undesired effects are assumed to be similarly frequent, almost the same in the severity, with dose-dependent for all three PDE-5i [4, 6, 7, 10-12]. Experience with sildenafil has shown that only a few patients discontinue treatment for a reason of visual changes as a

Table 1. The main camparison and cardinal differences between various type of common phosphodiesterase type 5 inhibitors (PDE-5i): Sildenafil, Vardenafil and Tadalafil.

The Properties and Characteristic Features	Sildenafil	Vardenafil	Tadalafil
1. Phosphodiesterase Type 5 Inhibitors Selectivity (PDE-5i) than the PDE-6i	Approximately three times more selective to PDE-5, *i.e.* more disturbances in the colour perception	Approximately three times more selective to PDE-5	700-fold more selective for PDE-5 than PDE-6, *i.e.* less effect on the transfer of light impulses into nerve impulses in retina
2. Molecular structure	Similar to Vardenafil	Similar to Sildenafil	Different from both Sildenafil and Vardenafil
3. PDE-11 selectivity inhibitors	Less selective to PDE-11	Less selective to PDE-11	Tadalafil is more selective for PDE-11 relative to PDE5 than sildenafil and vardenafil. Although PDE11 is expressed in numerous tissues, its physiological function remains to be explained
4. Bioavailability (%)	At the single 100 mg dose: 41	At the single 100 mg dose: 15	Not determined
5. Maximum plasma concentration (C_{max}) (ng/ml)	560	17	378
8. Time to maximum concentration (T_{max}) (h)	0.83	1.0	2.0
9. Percentage of the protein binding	96	95	94
10. Half-life, t½ (hours)	3.7	3.3–3.9	17.5
11. Duration of onset	Moderate	Faster	Longer
12. Benefirs over the adverse effect profiles	On demand, 'on and as' basis	On demand, 'on and as' basis	Not very much on demand, as a dose of 20mg tadalafil may be benefited for at least minimum two engaging sexual intercourse, *i.e.* maybe cost-effective
13. The duration of effect (hours)	4 – 5	4 – 5	36
14. Their 'nick-name'	'The earliest'	'The strongest'	'The longest'

side-effect [23]. Long-term studies with sildenafil have yielded no evidence of more extensive or permanent disturbances of the vision as a consequence of occasional PDE-6 inhibition [24]. The lumbago, myalgia and muscle pain are reported relatively frequently with tadalafil [25]. Tolerability of tadalafil is problematic: with daily oral ingestion, 7% of men in the 10 mg group discontinued treatment owing to side effects, 10% at 25 mg, 19% at 50 mg and 29% at 100 mg. With oral ingestion, tadalafil caused myalgia and backache in over 10% of those treated and dyspepsia and headache in over 25% [26]. Since all 3 PDE-5i are degraded down mainly *via* cytochrome P450 CYP3A4, a dose adjustment should be considered when given in combination with CYP3A4 inhibitors (*e.g.* macrolides, antifungal treatment agent like ketoconazole) [25, 26].

Like sildenafil, vardenafil has a modest hypotensive effect [4, 6, 7], maximal 5-10 mmHg average [10-12]. Tachycardia has been observed at a vardenafil higher dose more than 20 mg [4, 6, 7, 10-12]. Since peak vardenafil levels are 30% higher in geriatric patients and the **t½** is 25% longer [26], low dosages should first be prescribed in men who are prone to hypotension. At the high dose of 20 mg vardenafil, unwanted side-effects were observed twice as frequently in elderly patients [26]. Tadalafil, too, exhibits prolonged **t½**, *i.e.* 22 hours, in geriatric patients, where the tadalafil was still detectable 6 days after last ingestion. Furthermore, smoking and the body mass index had a weak effect on the pharmacokinetics of tadalafil, and also where food intake is concerned [27]. For vardenafil, serious adverse events like cardiovascular event have been reported in patients with comorbid diabetes mellitus (DM) with a ratio of the following - placebo: 1%, 10 mg: 2%, 20 mg: 3%, respectively [26]. In an FDA publication [28], a conclusive evaluation of spontaneous reports of mortality associated with sildenafil was undertaken. There is no evidence of an increased mortality rate among sildenafil users compared to the general population [29-32].

For all three PDE-5i the contraindications are almost similar [4, 6, 10-12]. Men whose sexual activity is not advisable on serious medical grounds like suffering from severe cardiovascular events *e.g.* immediately post-MI should not be prescribed with PDE-5i [33]. Since both sildenafil and

vardenafil have moderate vasodilator effects, they should not be prescribed in the presence of orthostatic hypotension, and PDE-5i should only be taken with caution when there is hypertrophic obstructive cardiomyopathy [4, 6, 7, 10-12, 26].

With the utmost inhibition of PDE-5 already achieved with sildenafil [34], an increase in efficacy is not to be expected with substitution to vardenafil and tadalafil. As yet, we need more data to review the adverse effects of vardenafil and tadalafil, mostly in long-term use and in high-risk groups. Sildenafil has already been prescribed in over millions of men in over 110 countries [4, 10-13, 34] and is one of the best researched pharmacological agents available. The post marketing statistics show a high degree of harmony with efficacy and safety data obtained in the clinical licensing studies [28]. This benefit in terms of fundamental facts regarding safety data makes the sildenafil a safe and reliable treatment for patients with ED. Whether tadalafil or vadenafil may be complementary to sildenafil or not will be shown the years following market establishment and wider prescription experiences [28].

8. THE FAILURES OF PDE-5i

There are reports of men who do not respond to PDE-5i treatment. Although available guidelines maintain that PDE-5i such as sildenafil, tadalafil and vardenafil are first-line pharmacological treatments of ED, approximately 30-40% of PDE-5i users fail to show a satisfactory response to therapy. Certain patients may be suffering from ailments such as neuropathy, DM or severe vascular disease, and with co-existence with psychosocial attributes and inhibitions, these maladies are associated with PDE-5i treatment resistance [35].

The role of men's sexual partners in EF is crucial in achieving sexual stimulation and satisfactory erections. The physiology of male and female sexual functioning may fit like a "pair of perfect gloves" [36] (Fig. **4**). It is evident that male sexual functioning is 'mirrored' by his partner, with approximately 43% of their sexual functioning dependent on each other's role [36]. This relationship is logical, as women who do not have satisfying SI due to their partner's ED will experience rejection, disillusion and may be unwilling to participate in subsequent sexual activity. Failure to stimulate the male sexual partner may decrease the production of NO *via* the dopaminergic-oxytocin-nitric oxide pathway and further impair his erection. This conundrum will become a vicious cycle affecting the sexual couple.

Other factors compounding treatment resistance of ED include, having co-morbid mental health problems and receiving psychotropic medication. Sexual dysfunction can be iatrogenic from psychotropics but also symptomatic of depression or anxiety dusorders. Iatrogenic ED can be caused by antidepressants (AD), mood stabilizers, antipsychotics and benzodiazepines [37]. Due to increase in the serotonin availability at the neuronal synapse from the serotonin-selective reuptake inhibitor (SSRIs), or serotonin-noradnenergic reuptake inibitor (SNRI), the serotonin will negatively decrease the dopamine level in CNS, disrupting the desire-arousal-excitement-orgasm performance [38, 39]. Psychopharmacological agents such as bupropion and mirtazapine also affect sexual function, albeit to a lesser degree compared to SSRIs or SNRIs [38]. Drugs to drug interactions in addition hamper usage of PDE-5i in several instances [4]. As patients are already suffering from complex diseases such as dyslipidemia, DM or hypertension, receiving statins and other medications, the use of AD, antihypertensives, and other medications will further impair their sexual functioning. For instance, patients with dyslipidaemia receiving statins may suffer from reduced libido affecting overall sexual performance [39, 40]. Patients with dyslipidemia and hypertension are also known to have poor vasculatr perfusion decreasing penile blood flow, inevitably reducing response to PDE-5i.

Besides the myriad co morbidities that contribute to treatment resistance with PDE-5i, there is additional data revealing that subtle, frequently neglected factors may contribute to the overall picture of pharmacotherapy failure. As highlighted earlier in Fig. (**4**), male sexual performance is also greatly influenced by their sexual partners. Visual cues, such as appearance and grooming, sensual caresses and erotic conversations and actions may enhance men's sexual performance [36, 42]. Patients are usually told that a PDE-5i does not guarantee erections in the absence of adequate stimuli and stimulation. Hence, it would be essential to include and educate sexual partners during therapy sessions regarding the importance of sexual stimulation and foreplay prior to SI.

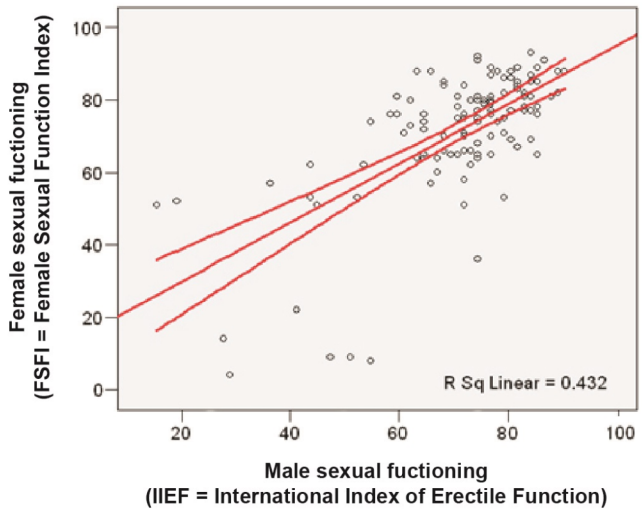

Fig. (4). The strong and positive correlation between male and female sexual function [36] ($r = 0.43$, $p < 0.05$) Adapted with permission from: Yeoh and Rosdinom *et al*. (2014).

9. THE MOST PREVALENT CO-MORBID SEXUAL DYSFUNCTIONS- ED AND PREMATURE EJACULATION (PE): WHAT ROLE DO PDE-5i PLAY IN PE TREATMENT?

The co-morbidity of both PE and ED is an established sexual problem in men [43, 44]. Shamini and Hatta [43] studied the association between PE and ED in an urban population. The prevalence of PE in men suffering from ED co-morbid with PE is 25%. There was a significant and strong association linking PE and ED. Chen *et al*. [44], interestingly reported that PDE-5i was an effective agent and has

a role in the treatment of PE. Plausible explanation on the therapeutic mechanisms of action of PDE5-i helping patients with PE is numerous and complex, incorporating the prefrontal-limbic-hypothalamic-autonomic interaction and neural networking [4].

10. OTHER PHARMACOLOGICAL AGENTS FOR ED TREATMENT: ARE THERE OTHER OPTIONS?

There are other treatment modalities available for ED besides PDE-5i. Alternative treatments range from non-pharmacological approaches such as psychotherapy to invasive pharmacological treatments, for example, alprostadil (prostaglandin [PGE-1]), which has been demonstrated to sustain an erection at a satisfactory rate [41]. Prostaglandin therapy is one treatment modality finding a popular place in the management of ED [42]. Prostaglandin acts by exerting vasodilatation of the corpus cavernosum of the penis, increasing blood flow to the region, resulting in erection. Another alternative form can be delivered *via* injection to the sides of the penis, resulting in a more sustained action. However, some patient reported priapism (Fig. **3**) due to prolonged, painful erection as a side effect [43, 44]. Prolonged administration can also lead to scarring and fibrosis of the penis and may hamper future erections [45]. Moreover, most patients find the idea of injections less enticing compared to oral medication.

11. A PATHWAY FOR SEXUAL INTIMACY AND SEXUAL SATISFACTION: THE ROLE OF PDE-5i

We propose a plausible model explaining the pathway for sexual intimacy incorporating PDE-5i. In the model, we emphasize the importance of sexual stimulation in relation to time. To the psychiatrist, the concept of the sexual response cycle is applicable in understanding the clinical challenges encountered during ED treatment. There appears to be two levels of sexual response significance in the model, the first being the point of 'reaction' to sexual arousal threshold and the second being the point of orgasmic threshold. In other words, level of sexual arousal has to reach a particular level before propagation to the next level, so that orgasm can occur [46]. When an individual is exposed to sexual arousal, such as through foreplay, sexual interest develops, and if sufficient, the man will show a psychophysiological response. If sexual stimuli are non-persistent or not perceived as sexual cues, sexual desire may quickly fade and penile tumescence subsides (Fig. **5**). With the assistance of PDE-5i, sexual stimulation can reach a point of satisfactory erections for SI, and subsequently orgasm (Fig. **5**).

Various points in the threshold model become critical in a couple's endeavour to reach the desired summit. Unfortunately, most levels are easily disrupted, especially in older adults. Reaching the first point of sexual arousal by itself would be challenging for a couple, particularly for men over the age of 45 with dyslipidemia and on statins known to decreased libido [49]. The point of intercourse initiation, the level after sexual arousal in the postulated model, is affected by several factors in both male and females [50, 51, 54].

For men, when ED becomes the main factor of frustration and disappointment when desire occurs, his partner will be also unhappy. The inability to penetrate will further deter his partner's sexual desire, *e.g.* beginning of inadequate vaginal lubrication leading to difficulty of penetration, despite sufficient erection from the male counterpart [51, 52]. Not all men with ED fail penetration altogether. Some attain erection sufficient for initial penetration but lack the vitality to sustain and endure. Alike a "boxing match," the men may have more probabilities of winning the 'battle', if the 'match' is continued, with few initial failures (Fig. **6**). As the male partner fatigues and erection fades, so does the level of sexual stimulation. Orgasm does not occur in this scenario as the level of sexual arousal elicited *via* intercourse was insufficient to attain the minimal threshold. In such cases, PDE-5i treatments are able to rectify the shortcoming by providing a sustainable erection.

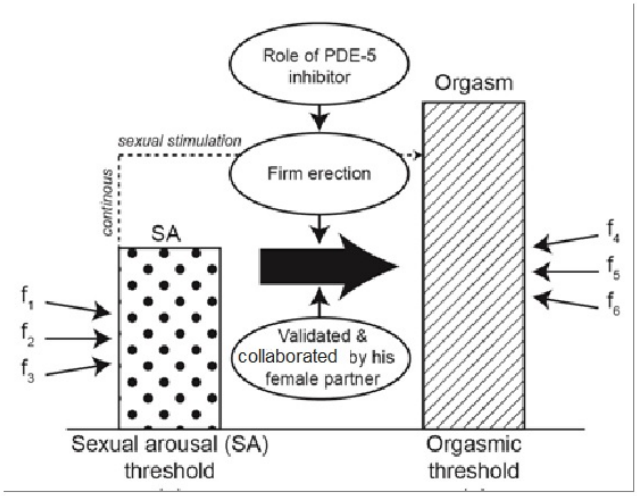

Fig. (5). Factors that may influence the sexual arousal (SA) and orgasmic thresholds. This relationship postulates that the SRC (sexual response cycle) is quanta in speculation where each threshold is contributed by different factors, for example: f1 eg. Androgen / Testosterone positive hormonal influence; f2 eg. sexual fantasy; f3 eg. permissive ambience f4 eg. oxytocin release; f5 eg. good pelvic thrust; f6 = eg.. no external/ outside distraction.

Practical steps on how a psychiatrist can help the patient with ED are based on the conceptual model framework from (Fig. **5**) considering arousal and orgasm thresholds. The intricate role that both partners play during a sexual relationship and how one-factor affects another in the context of ED management is proposed in the next (Figs. **6** and **7**).

The cycle begins at the far left of the illustration in (Fig. **6**), with the couple engaged probably in a loving/ romantic situation. The emotions of lust/ love and the longing for sex originates from the activation of the limbic system and leads to the sense of emotional intimacy and sensual feelings. This may be coupled with the sense of 'being together' to activate a male's sexual drive. It is also a well-known fact that the sight of the female partner's body parts and degree of exposure as well as personal fantasies play a role in activating a male's sexual drive [53]. Conversely, the female counterpart is more receptive to sexual stimulation and foreplay, requiring more time to become sexually aroused and participate with the sexual activity [53-55]. After successful intimacy and foreplay, a couple would experience sexual arousal and desire to engage in sex [54]. This phase is where adequate

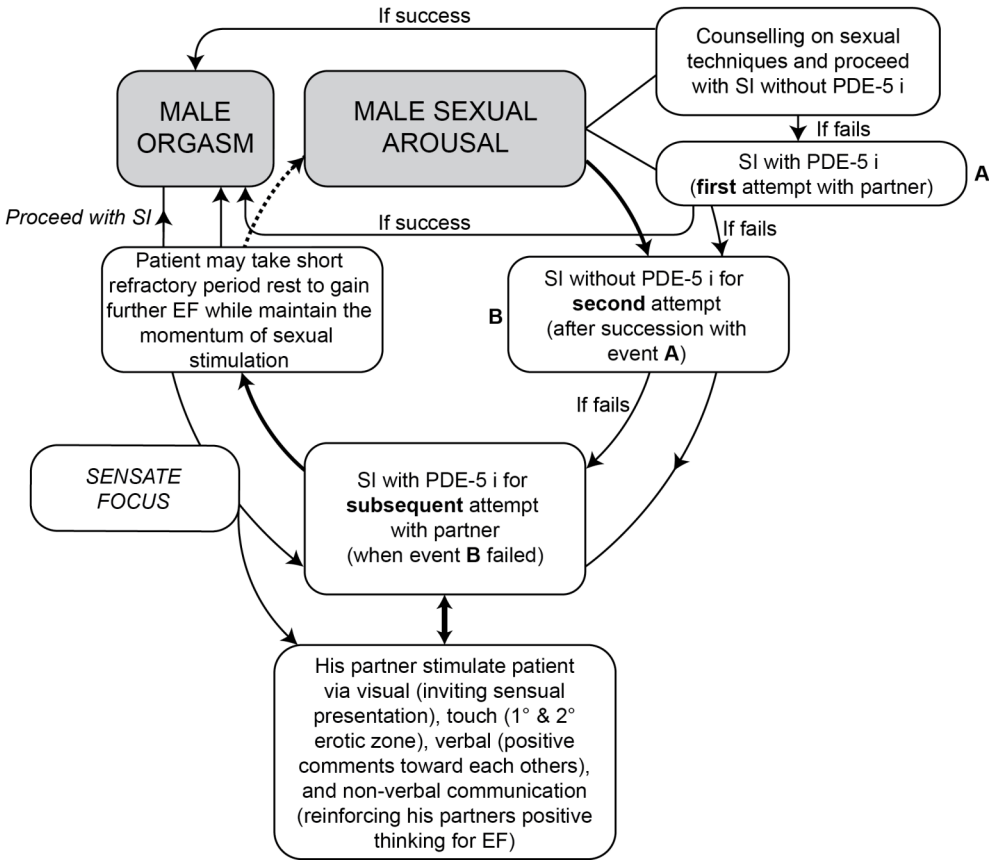

Fig. (6). Practical tips for patients with Erectile Dysfunction (ED) engaging in sexual intercourse (SI): The role of phosphodiaterase-5 inhibitor (PDE 5 i).

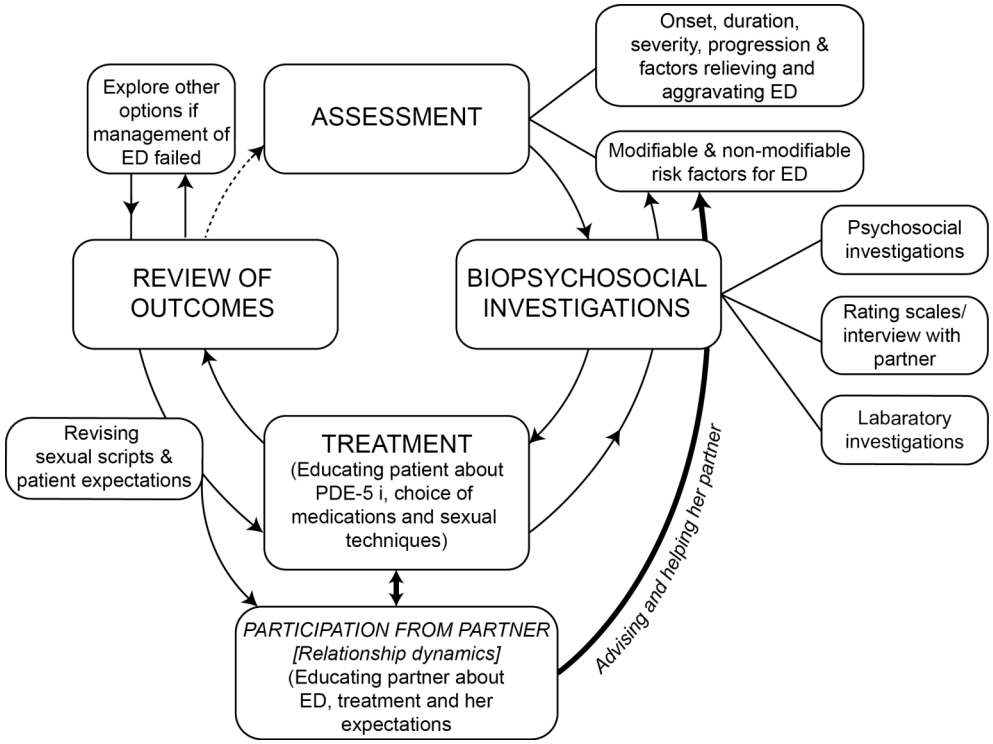

Fig. (7). The pivotal management challenges for men with ED – assessment of problem and treatment for ED. The role of patient's partner is crucial for their sexual endeavour.

and sustained erections become a critical factor. If erection is inadequate, or fatigue inhibits EF, men may take PDE-5i to have a good erection prior to SI, which could result in orgasm for the couple.

The main problems commonly encountered by treating doctors in clinical practice are not only dealing with patient's frustrations as results of failure in achieving orgasm due to ED, but also the sequelae of low sexual arousal and desire (resulting from poor EF). In this model, patient may attempt SI naturally after applying proper sexual techniques *via* counseling and psycho education beforehand [53]. If there is a failure, patient may attempt SI with the aid of PDE-5i (Event **A**). Once the initial attempt is successful, then the subsequent SI can be performed by the patient without the use of PDE-5i (Event **B**), where patient building second success over the previous victorious experience. Some patients may have self-confidence to accomplish sexual performance without a help from PDE-5i [53]. At this juncture, the female counterpart plays an important role, *e.g.* prompt sexual stimulation *via* visual (inviting sensual presentation); touch (over primary [genitals] and secondary erotic [non-genitals] zones); and verbal communication, *e.g.* warm and loving comments that reinforce partner's positive thoughts towards EF [54]. At any point after Event **B**, patient may also take a short reprieve to regain EF while maintaining the momentum of sexual endeavour. Sensate focus intervention, a therapy that allowed patient to explore their own unique personal sexual gratification can be employed to enhance the EF, increasing chances to attain a coveted orgasm [55, 56]. It is imperative to educate the couple how to apply this cycle of techniques in practice where the couple aims to attain and maintain erection, with or without pharmacotherapy, taking pauses for rest and applying sexual stimulation whenever necessary until orgasm is attained.

12. THE FRAMEWORK FOR MANAGEMENT STRATEGIES IN PATIENTS WITH ED: THE PSYCHIATRIST'S PERSPECTIVE

When a man suffering from ED visits the clinic, he will be recommended to undergo an initial assessment including psychosocial investigations and laboratory tests (Fig. **7**). During psychosocial investigations, the therapist should explore the onset, duration, severity, progression, aggravating and relieving factors related to ED [45, 54-57]. It is pivotal to determine how the ED affected him, his marital, sexual and relationship dynamics and if there is a presence of psychiatric co-morbidity. At the same time, identifiable modifiable factors [57] associated with ED like body-mass index, level of work-stress, expressed emotion [18, 19, 45, 54, 57] and level of marital satisfaction [45, 54] need to be recorded to help the patient to understand and remedy EF.

The sexual satisfaction and gratification experienced in SI are then encrypted in the memory circuit pathway, making the person more motivated and confident for the next SI cycle. The treatment success rate can be increased by frequent PDE-5i intake to cement self-esteem [55]. In simplified terms, the learned behaviour in this context is that intimacy, and proper foreplay leads to receptiveness in female and proper erection in male, especially with the aid of pharmacotherapy. Some men with ED will experience improvements in self-esteem improvement and self-confidence [48].

Multiple failures of highly desired SI attempts inevitably lead to frustration in the couple, and that becomes encrypted as well, turning the cycle into a vicious negative outcome. Male partners may even develop performance anxiety, further hampering subsequent erections due to the anticipation and fear of failure, and another negative cognitive automation [5, 52, 54], while females tend to feel upset making them psychologically less receptive.

Men in late life inevitably encounter ED from organic causes such as a complications from degenerative diseases like DM and dyslipidemia. They will benefit from both PDE-5i treatment and psychotherapies [56]. These patients may require treatment modalities targeted at the underlying unconscious conflict and psychodynamic issues, albeit elderly patients are usually less psychologically-minded or unwilling to change, making CBT and uncovering psychotherapy approaches very challenging [58]. Another group of patients frequently encountered are those who are not inclined to accept pharmacotherapy, preferring the process of recovery in natural ways. In these cases, many are keen on attempt, and frequently respond to psychotherapy offered by psychotherapists/treating doctors [58]. In short, psychological interventions remain important in treatment of ED but the selection of a suitable patient for these therapies would require consideration of age group, underlying medical ailments and patient's personal preferences.

There are several dimensions assessed in this context. Psychosocial dynamics play a huge role in a healthy sexual life and undergo assessment by interview and probably a rating scale, an International Index of Erection Function (IIEF) to assess clinical progress [58]. The patient is then subjected to lab investigations and associated blood parameters as well to determine the level of physical fitness and to pinpoint any comorbidity that might have led to ED [59]. Patient's partner would be engaged at this point in view of the imperative role of the female counterpart [47]. Once we pass the initial formalities of the basic assessments, the patient is given counseling regarding the role and side effects of PDE-5i. Discussion at this juncture involves cost factors, which is an important determinant of patient adherence [60]. Treatment alternatives such as prostaglandins are also made known to the patient. Success rate is enhanced by offering counseling regarding proper sexual techniques as well [61, 62]. After administration of psychopharmacological therapy which is a combination of various therapies of medication and counseling mentioned, treatment response is then evaluated. It has to be noted that the cycle of management is 'two ways' implying the need to turn back to previous steps of management in the event of treatment failure at any given point. One-note worthy point here would be the role of patient's partner who is imperative to consider in overall sexual performance [63, 64]. Hence, if there is repeated treatment breakdown or unsatisfactory response, it would be wise to re-evaluate the role of the patient's partner (demarcated by the bold curve in the chart). The therapist needs to re-evaluate again the spouse's attitude and support for the patient, seeking to uncover any amenable factors such as critical comments/ harsh remarks, *etc*., which harkens to the deterioration of sexual function [65, 66]. Ideally, every adjustment of therapy should be followed by review of outcome. If treatment is still unsatisfactory, one might consider other

optional treatment modalities mentioned earlier. If a response is favorable, patient would be given follow-up and monitored regularly to identify development of any biopsychosocial tribulation that may hamper sexual function.

13. NON-PHARMACOLOGICAL OPTIONS FOR TREATMENT: COMBINATION WITH COGNITIVE-BEHAVIOR THERAPY (CBT), BEHAVIOUR THERAPY AND OTHER PSYCHOTHERAPY MODALITIES

CBT and other psychotherapy modalities were used for the past few years with favourable success rate for men with ED [56]. Many men suffer from problems such as anxiety from previous failures and poor performance in bed whilst some other encounter ED due to depression, stress or fatigue from work [5, 50]. CBT and other psychotherapies work well in this context and can even be coupled with pharmacotherapy for those who demonstrate fewer responses in their erectile function [5, 50, 58]. Psychotherapy works by instilling hope and providing support when emotional distress is a consequence of ED. CBT works by restructuring the cognitive errors internalized from sexual encounters, *e.g.* catastrophic thinking of erection failures. Psychodynamic approaches may uncover past and present conflicts related to sexual fantasy or actions that interfere with current sexual health.

CONCLUSION AND RECOMMENDATIONS

ED is notably a distressing medical disorder, with underlying pathology of penile arterial narrowing that not only impairs erections due to low blood perfusion, but also have a negative emotional impact in patients and their partners. In addition to ED being an indicator for underlying cardiovascular morbidity, and possible mortality, it also plays a role as a barometer to test the romantic and sensual elements of conjugal relationships. As ED becomes apparent with advancing age and developing medical co-morbidities, the PDE-5i have a pivotal role in restoring satisfying EF, leading to the enjoyment of sexual relationships. While PDE-5i work well in most patients, failures are also reported, and it is postulated that lack of sexual stimulation and partner's role - inadequate sexual participation - along with other factors such as being fatigued, in a stressful state or suffering from serious physical disorders, make up the interplaying factors of this multidetermination condition.

All PDE-5i are equally efficacious and long-term use will be not only beneficial to longevity due to their inherent vasodilator properties, but also have an advantage in boosting self-confidence and psychological readiness with successful erections that enable sexual health. Indeed, PDE-5i have catalyzed the revolutionary perception of how we are seeing sex as an essential part of life even in late life. As benefits usually outweigh risks, PDE-5i had an important place in the psychiatrist's treatment armamentarium to improve patients' sexual health and quality of life.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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