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Considerations for Prescribing Pharmacotherapy for the Treatment of Erectile Dysfunction

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Abstract:

Introduction: The effectiveness of phosphodiesterase type 5 inhibitors (PDE5i) in treating erectile dysfunction (ED) creates a new field of both medical practice and pharmaceutical manufacturing. Both paved the way for emerging of minimally invasive therapies to restore male sexual function. However, what is the best drug to achieve the optimum outcome is still a challenging question to be answered.

Areas covered: The general viewpoint of matching the pharmacotherapeutic characteristics with the patient's medical, social and psychological variables, in order to balance between efficacy and safety. Several studies had investigated considerations for preference and long-term adherence for PDE5i. However, thorough investigation of considerations for prescribing ED pharmacotherapy are still lacking in literature. This is the aim of this manuscript.

Expert opinion: Several issues should be considered in the planning of ED management such as, the patient's and partner's expectations, etiologic considerations, performance status, safety, adverse effects, ease of administration, compliance, bad experiences with previous treatment, availability, cost, social factors, satisfaction and finally, regimen considerations. Addressing the patient's and partner's individual needs help to tailoring treatment in order to minimize compromises and optimize gains.

- Keywords: Erectile Dysfunction, Pharmacotherapy, Considerations for Prescribing Treatment

1. Introduction:

ED is defined as the inability to initiate and/or maintain sufficient penile rigidity to have satisfactory sexual intercourse [1]. Though it can be secondary to other medical phenomena associated with other systemic diseases or a part of multi-organ dysfunctions [2], it can also be a primary complaint and reflect non-medical issues related to the social and psychological life of the patient [3, 4]

Since ED affects the personal, psychological and social aspects of life including self-image and relationship with the partner, therefore it is considered as an important representative of quality of life (QoL) [5, 6].

The most common organic causes of ED are vascular impairment and endothelial dysfunction that may result in the failure of vasodilation, which would cause blood to enter the corpus cavernosum and restrict venous output giving the penis rigidity [7, 8]. The first-line treatment of ED includes oral pharmacotherapy, vacuum device (VED), and topical or intra-urethral preparations. The second-line treatment is intra-cavernosal injectants (ICI). Penile prosthesis is the third-line treatment and is characterized by the irreversibility. The approach to be taken for the management of non-responding cases is to consider a plan of graduated interventions prioritized on the basis of patient's characteristics and continuous re-assessment and participation in decision-making [9, 10]. The Selection of the suitable line of treatment needs an integrated approach of thinking that should be kept in parallel with the dynamic process of diagnosis, treatment and monitoring of ED patients.

Preference and long-term adherence for oral PDE5i have been investigated in several studies using a longitudinal approach and discussed certain molecules and their features [5, 11-15]. In

daily practice, it is of utmost importance to know how to select a particular drug across the whole range of available pharmacologic treatment. In the current article, we have addressed the basic rules of designing a therapeutic plan for ED patient. Furthermore, we have discussed factors and considerations that affect this therapeutic plan.

2. What should be considered when treating ED? (Table 1, Figure: 1)

2.1. Physician *versus* Patient and Partner Prospect (Table 1, Figure: 2)

ED reflects the convergence of various subjective views by multiple participants with different standards. Those participants are: patient, partner and physician [5, 16]. Although objectivity can be fulfilled by the physician via a wide range of clinical tests, the clinical judgment through treatment pathways can always be affected by the other two participants [15].

Physiologically, sexual intercourse is a safe and spontaneous activity. It is meant to end up with reproductive and/or self and partner-satisfaction outcomes [17]. Hence, the optimistic target for the purpose of treating ED should be achieving a “satisfactory sexual performance within safety conditions”. Occasionally, this aim cannot be fully achieved. There is always a sub-optimal situation that includes only part of these 3 factors; satisfaction, performance or safety [18-20]. However, the preference of the therapeutic plan usually depends on the better matching between patient-partner-physician views and satisfaction-performance-safety profile. It is interesting to note that any therapeutic plan is not just using a monotherapy of oral medication or a sequence of scheduled injections. Instead, it is a dynamic process of forward-backward and forward again in an algorithm of assessment and treatment measures.

2.2. Performance: Sexual performance is an integration of *biological efficacy* and suitable *social circumstances* [20, 21]. It is evident that suitable circumstances of intimacy and

stimulation are critical in both physiologic and drug-enhanced erection [22, 23]. To achieve good rigidity, both aspects should be available and factors that affect both should be addressed.

2.2.1. Biological Efficacy: Erectile function is the product of integration of multiple systems (vascular, neural, hormonal, and metabolic) [24]. Etiology is an important consideration as a part of the diagnostic workup [25]. The primary etiology can be curable, e.g. hypogonadism or arterial injury, or incurable, however, modifiable in most of the cases. Diagnosing curable conditions and initiating the proper treatment can improve the outcome and even preclude the requirement of further intervention [26, 27]. Considering screening for modifiable risk factors and medical co-morbidities, e.g. smoking, obesity, sedentary life style, diabetes, hypertension and atherosclerosis, as a basic step in the diagnostic workup can guide the treatment into more effective measures and can improve the outcomes [28, 29].

2.2.2. Social Circumstances: If the treatment cannot improve erectile function within the suitable time frame, it cannot be considered as effective or useful. The same applies if the desired treatment effect persists far beyond of being needed. In this situation, the social and mental readiness is the keyword. So, the patients can administer that treatment in the optimum time to achieve the best biologic effect. This virtual condition cannot be fulfilled in all cases [12].

2.3. Therapeutic Regimen: The therapeutic regimen relies upon the drug route of administration, dose and duration. In addition, the invasiveness, adverse effects profile, and cost are also main considerations. The dose might be on demand or on a daily basis. Also, the duration of treatment should be considered whether to be short or long. Most of these factors are related to the pharmacokinetics, so, for example, the longer duration of action of tadalafil gives it an advantage over others in terms of the use for daily dose regimen [30].

2.4. Compliance: Compliance of the patient to treatment is affected by the durability of the satisfactory effect but more by the tolerability of side effects [31, 32]. Maintaining compliance is related to continuous monitoring. Consider the continuous monitoring as a factor itself that enhances compliance along with further modification of therapeutic plan based on response [33]. The follow up of patients who are respondents to pharmacological treatment should emphasize the maintenance of efficacy and safety [34].

2.5. Previous Bad Experience: A failed trial of one drug outlines one of the reasons for discouraging trying new treatments. An early successful attempt of intercourse is predictive of further successful therapy [35]. Progressing into further types of erectogenic medications should be in a justified pre-planned approach. As mentioned, it is very likely that one failure may affect the treatment plan. Even successful treatment is not a guarantee of having better satisfaction by adding new drugs [14, 18].

2.6. Adverse effects: Adverse effects should be considered starting from the level of evidence that relates a particular sign to a particular drug, the dose and duration of treatment, associated morbidities, and the tolerability of each patient to unpleasant complaints. Many side effects occur due to the interaction of drugs with altered physiologic functions such as a preexisting chronic illness, or with other pharmacologic and non- pharmacologic agents [36-37].

2.7. Life style modification: Measures used to promote the general health profile also affect erectile function and ED patients in a positive way. Increasing exercise, consuming healthy diet, losing excess weight [38], and cessation of smoking have all shown an improvement of the erectile function [39]. The evidence of the effect of lifestyle interventions on ED patients ranges from observational studies to systemic reviews and meta-analyses [18, 26, 40]. Men with comorbidities, e.g. diabetes and cardiovascular disease, have double benefit from controlling

lifestyle risk factors [41, 42-44]. Therefore, in the effort to optimize the outcomes of medical treatment, lifestyle modification should be a part of our consideration in diagnosis, treatment, follow up and analysis of failed treatment [28, 45].

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3. Etiologic considerations

In curable cases, a definitive therapy is targeted with a high possibility of reversing the ED status with a maximum achievement of efficacy and spontaneity within acceptable safety levels. In the non-curable cases, the main aim is to regain a near-normal sexual life and all etiology-specific measure might help to modify the course of the disease.

3.1. Curable causes of ED: the ED caused by testosterone deficiency, arterial injury or psychological disorder can be managed with the intent of cure.

3.1.1. Testosterone Deficiency (TD): can be due to a primary testicular failure. However, pituitary and hypothalamic diseases can contribute to a significant portion of TD cases. Hyperprolactinemia from a functional pituitary adenoma is a diagnostic challenge for the clinician managing a case of ED [46, 47]. The decision of testosterone administration in ED patients should be based on clinical data and a precise determination of testosterone level [48, 49]. For patients with TD, testosterone supplementation (TS) increases the chance of success of PDE5i in non-responders [50]. The relationship between TS and harmful effects on cardiovascular functions is not proved with high-level evidence [51-53]. There is also no recommendation that TS is beneficial for cardiovascular outcomes [54]. However, TS is contraindicated for patients with current or history of prostate cancer [55]. There is no adequate evidence to confidently exclude this risk. Although the level of prostatic specific antigen was not significantly changed after 1 year of TS in patients with hypogonadism associated with ED [56].

So, for ED patients who are candidate for TS, digital rectal examination, prostate specific antigen and even biopsy, if needed, are essential before institution of TS [56]. Patients with TS should be

monitored for hematocrit, hepatic function and lipid profile. TS is associated with various range of adverse effects that mandate close monitor with meticulous clinical and laboratory checks [53-57]. While testosterone replacement has traditionally been reported to be contraindicated in men with prostate cancer, recent studies have questioned this concept. Since testosterone deficiency is associated with negative effects on quality of life, testosterone therapy became essential for patients with hypogonadism, especially with the favorable pathology, who were treated and cured from prostate cancer [58, 59].

3.1.2. Arteriogenic ED: Perineal trauma is the main underlying etiology of arteriogenic ED [60]. This can happen in any age, however younger ages get better benefit from surgical treatment. The condition can be detected using Doppler ultrasonography and confirmed using penile pharmaco-arteriography [60]. The penile revascularization technique is associated with a success rate between 60% and 70% [60]. The optimization of this technique can be better achieved by the preoperative use of Doppler ultrasonography, cavernosography or cavernosometry to exclude veno-occlusive dysfunction [60].

3.1.3. Psycho-sexual issues: The aim of etiologic considerations in this situation is to find out motivational obstacles. Combining psycho-sexual therapy with pharmacological treatment is associated with improved outcomes [61]. The psycho-sexual therapy includes; systematic anxiety reduction, interpersonal therapy, sensate focus, cognitive behavior therapy, sex education, couples' communication and sexual skills training [62, 63]. Usually, this is the role of the psychiatrist. With some preparation, the urologist can approach a "biopsychosocial" model with selected cases, which includes counseling about normal functions and education about helpful behaviors [64].

3.2. Non-curable causes of ED:

Microvascular and endothelial dysfunction associated with atherosclerosis plays an important role in pathogenesis of non-curable ED [8]. Since cure is not available, the pathogenic process that leads to ED is still on action. The control of the associated molecular derangement and medical co-morbidities improves the outcomes of medical treatment in the short and long term [8]. Patients under chronic medications are liable for serious interaction with ED treatment [65]. The same occurs if the PDE5i levels are reduced by either hindering absorption or enhanced metabolism, so that the false impression of non-response leads to escalating the dose, changing medication or shifting to a surgical management [65]. Accordingly, the atherosclerotic changes that start in a systematic manner all over the arterial system will progress in a similar pace and so occlude smaller arteries before larger ones [66]. With the contiguous exposure of harmful risk factors like obesity, smoking and unhealthy diet, the ED can be an early sign of coronary artery disease [42].

4. When the PDE5i should be considered as a first line of management? (Figure 3)

(Dynamic interactive approach)

4.1. How could ED be treated dynamically and interactively? The need for a dynamic interactive approach in treating ED patients reflects the wide range of therapeutic measures and variable responses to them. Since the way of ED presentation is not usually consistent among patients and patient's view of the problem cannot be measured against a scale, it is unwise to pursue a standard of care for all patients. The definition of a successful trial, a good response and a failure of treatment is different from a person to another and even in the same person with different partners or different contexts. Analyzing this field has raised the need for a dynamic tool to both treat and follow up satisfaction for each patient [9, 10, 67, 68]. In this approach,

there is always a starting point based on an initial matching between patient-partner-physician views and the therapeutic regimen.

The assessment of the ongoing point, i.e. targeting the common causes of failure, checking the basic determinants of maximum biologic efficacy, and re-adjusting the regimen by drug, dose and timing factors, is the key-point of the right direction. Following a bidirectional move; forward with successful aspects, backward for newly discovered issues and re-figuring the complete picture of a patient's problem; will be helpful. The endpoint is to have a satisfactory and safe performance.

4.2. What should be considered while approaching ED patients? (Figure 3) the arrangement of erectogenic agents in a dynamic regimen should consider some important points [67-69].

4.2.1. Patient's preference: The well-educated patient can show preferential selection for a specific line of treatment or even name one medication. The physician's role is to emphasize on drug use, side effects and efficacy. The history of failure might be due to the incorrect use or the ineffective dose delivery and should be considered if the patient relies on these false experiences [67-69].

4.2.2. Invasiveness: Most of patients tend to prefer less invasive measures starting with oral medications, leaving injections or VED for a later stage to avoid unnecessary discomfort or side effects. However, the selection between invasive and non-invasive treatment should be based on patient's informed education, the meticulous definition of patient condition, and matching with patient's medical and sexual characteristics [67-69].

4.2.3. Ease of administration: The feasibility of administration is important to achieve a sense of natural performance. The failure of treatment can occur due to invasiveness and the

requirement of physical dexterity of the patient, i.e. to manually apply a topical agent, ICI or intra-urethral inserts. Furthermore, the inadvertent injection into urethra or long-term use of constriction ring after VED can be the main complaint of a motivated patient who uses these methods [67-69].

4.2.4. Re-assessment: The counseling of ED treatment should be based on continuous patient encounter using scheduled and structured re-assessment. Web-based consultations or random telephone calls may not offer a good solution for every patient, however these methods have become essential in certain circumstances such as in the period of COVID-19 pandemic. Medical recording and institutionalized care are valuable tools to implement an effective long-term therapeutic care. The follow up with a single physician allows for a deeper understanding and involvement into the couple views and needs [68, 69].

4.2.5. Reversibility: Intuitively, the more structurally and functionally irreversible the treatment is, the later it should be introduced to the patient. The use of irreversible solutions, e.g. penile prosthesis, should be preserved for cases that show no response to other lines [67-69].

4.2.6. Availability: The availability might be the main obstacle against long-term regimen, using daily doses of certain oral agents, or ICI of vasoactive materials. Rationally, we should start with medications that can be accessed easily by the patient. Following the international guidelines might not be suitable in all countries because some of the recommended drugs are not worldwide available [67-69].

4.2.7. Cost affects compliance: Sometimes, this factor is a limiting factor of providing the most proper ED treatment, especially in patients with limited income. Hence, whatever the source of

patient's health care system is, it is better to start with the cheaper agent if available to ensure the compliance with treatment [67-69].

4.3. Why are PDE5is most commonly used as a first line?

Having one oral pill before intercourse allows for on-demand style and also for long-term daily use with tolerable side effects. Furthermore, PDE5is are available worldwide in affordable costs [27]. Fortunately enough, all PDE5is share almost a similar mechanism of action through the enhancement of NO signaling, increasing the cGMP, and ultimately producing smooth muscle relaxation [27, 70, 71]. Also, the PDE5is share almost similar side-effect profiles [27] and similar efficacy within similar contexts. This allows for interchanging between different drugs in cases of intolerability or a particular indication or preference [27, 70, 71].

4.4. What kind of PDE5is should be started with?

There is no standard oral PDE5i to start with. The response to one drug is not a predictor for the response to other drugs [9]. However, there is no significant difference in efficacy between the main 4 PDE5is; sildenafil, vardenafil, tadalafil, and avanafil. The differentiation depends mainly on the associated side effects or the matching between patient's requirements and what is allowed by the pharmacokinetics of the drug [9].

Adding more drugs to this family such as Udenafil, mirodenafil and TPN729MA may help reserve more invasive treatments for a limited unsatisfied group of patients with restricted naturalness and spontaneity. Udenafil is a selective PDE5i that is safe and well-tolerated agent for treatment of ED. In comparison to placebo, Udenafil is associated with a significant improvement in the International Index of Erectile function (IIEF)-EF, Sexual Encounter Profile (SEP)2 and SEP3 [72]. The daily dose of Udenafil was subjected to randomized trials, and

showed similar benefits on IIEF-EF, whatever the baseline level of erectile function is [73]. Mirodenafil is a new selective PDE5i. It showed efficiency and safety in a wide range of ED patients in randomized placebo-controlled trials [74]. TPN729MA is also a new selective PDE5i that is characterized by long duration of action. In comparison to the vehicle in an experimental study, TPN729MA is associated with a significant increase in intracavernosal pressure in randomized groups of rat and dog models [75].

4.5. When to bypass this approach?

Psycho-sexual consultation can be used as a first line of treatment. This is considered when patient's evaluation reveals a relationship of ED with a primary psychiatric disorder. In some cases, the resolution of personal conflicts between couples can improve the sexual performance and satisfaction of both of them [16, 62]. The patient's wish is an important cause to bypass the use of PDE5i as first line.

Counseling the patient should include the side effects of each line, the success rate, the degree of invasiveness, and the demand for self-injection or device application. Informed decisions help in compliance and inter-partner cooperation [11].

4.6. What are the other lines and combination therapy?

The pharmacological treatment includes using alprostadil via intraurethral or ICI route. Usually, these lines are more invasive and kept for those patients who failed to regain a satisfactory sexual performance on PDE5i. They can be also used in patients with contraindications for oral PDE5i [76]. VED is a conventional technique that still has a place in the armamentarium treatment of ED. For selected patients, the VED can provide an acceptable outcome with good safety profile.

However, all these measures need well-educated and motivated patients with good mental and manual dexterity [77, 78].

As a combination therapy, the VED was added to PDE5is as a salvage in non-responders. The combination therapy is associated with a significant increase in IIEF-5 and the improvement of SEP-2, SEP-3 and Global Patient Assessment Scale (GPAS) responses in 79%, 70% and 74% of non-responders, respectively [79]. Furthermore, the PDE5is are used in combination with VED in patients with ED after radical prostatectomy. In comparison to non-intervention and monotherapy regimen with daily sildenafil, the combined sildenafil and VED regimen on daily bases is associated with better IIEF-5 in a 12-month follow-up [80].

Low-intensity extra-corporeal shockwave therapy (Li-ESWT) is a growing tool of managing patients with ED [81]. Li-ESWT can be considered for non-responders in combination with PDE5i. Investigating non-responders with vasculogenic ED shows a significant improvement in IIEF-EF and successful intercourse, and achieves full rigid penis in 70%, 68% and 35% of patients, respectively, after 1 month of combination treatment. There is also relevant evidence of significant changes in penile Doppler parameters. [82].

Several lines of stem cells have shown to have a high safety and effectiveness profile in management of ED in both animal models and humans [83]. There is a paucity of literature about whether PDE5i is beneficial for patients before or after stem cell transplantation. However, PDE5i is crucial in in-vitro preconditioning of cell lines prior to transplantation [84, 85].

Platelets-rich plasma is another cellular therapy that has proved to be safe and effective in patients with ED [86, 87]. This technique is still lacking standardization of procedure and dose

[86]. The role of pharmacotherapy in supporting patients after transplantation of cellular therapy needs further investigation.

4.6.1. Herbal supplementation

One of the most rising considerations on the daily practice with ED patients is the use of herbal supplementations. Conclusively, the use of herbal supplementations in ED patients is characterized by the following facts; many products may get into the market without fulfilling strict efficacy or safety guidelines, the available data do not support the use of a special herbal product and the comparability with PDE5i or other lines, and finally, there is a special pattern of acceptance among ED patients, especially online orders for PDE5i non-responders, without medical advice [88, 89].

Ginseng is associated with a significant improvement of erectile function in many studies [88, 89]. *Pinus pinaster* and *Lepidium meyenii* are associated with positive effects, however, less powered. Studies investigated saffron and *Tibulus terrestris* showed more heterogeneous data. However, formulations of combined agents are common [88, 89].

5. Regimen considerations:

Regimen considerations should be remembered through the process of diagnosis and treatment planning. As long as the prescribed drug is the final outcome of whatever approach a clinician follows, the common and special characteristics of each drug should lead that approach [90].

5.1. Considering interval between pill intake and sexual act: One of the most important real-life applications of pharmacokinetics is the ability to anticipate the time of maximum functional gain from a particular pharmacological agent. Most agents reach a peak plasma levels between 45 and 120 minutes. The failure of sexual attempts should be investigated for too early or too late

sexual act. Tadalafil reach maximum observed concentration in a range of half an hour to 6 hours, so despite having some specific advantages, this pill should be taken a long time before intercourse if taken in on-demand regimen [71, 90].

It should be noticed that effective spacing between pill and sexual act means scheduling sexual intercourse. Planning sexual intercourse by date and usually with hour are the main characteristics of the respondents to PDE5i [91]. However, a patient with a lifestyle of unplanned sexual intercourses or inability to get prepared several hours before them will complain of ineffective treatment, while it is not true. A patient with this kind of lifestyle may benefit from daily dose regimen of PDE5i.

5.2. Dose adjustment with food: It is important to make sure that PDE5i naive and patients who complain of ineffective or irregular efficacy of oral treatment are aware of the relationship between the drug action and food. Most of the PDE5is are affected by food except for tadalafil. Food delays the effect of sildenafil, avanafil and others [92, 93]. Fatty food reduces the absorption of the drug. Patients should be educated that maximum effects are going to be observed if the drug is taken in fasting state and longer spacing is needed otherwise [9].

Time to maximum plasma concentration depends on the rate of absorption via oral route. Taken on fasting state, sildenafil achieves maximal plasma concentration within 60 (30 - 120) minutes, vardenafil within 50 (30 - 120) minutes, tadalafil within 120 (30 - 360) minutes and avanafil within 30 – 45 minutes [93, 94, 95]. Oral dispersible preparations of sildenafil [96] and vardenafil [97, 98] did not improve this parameter significantly, however it bypassed the negative effect of meals.

Reports showed that avanafil has the fastest start of action, while few reports showed a satisfactory response within 15 minutes of vardenafil intake [97]. Regarding the rapidity of action, ICI of alprostadil can be superior to oral agents (effect starts 5 – 15 minutes from injection), although it includes invasive technique and higher rate of inconvenience [99-100].

5.3. Considerations regarding the duration of action:

5.3.1. The importance of duration: The effective window of PDE5i is the time on which the desirable effect on erectile function is anticipated. There is a relationship between the duration of action and the half-life of each drug. The interaction of other administered drugs for other comorbidities modify these durations [101].

5.3.2. What is the duration of action of each drug? Sildenafil and vardenafil have a half-life of about 4 hours duration. Sildenafil and vardenafil have an effective window of 6 – 8 hours [102]. Tadalafil has an effective window of 36 hours, as its half-life is as long as 17 hours. Avanafil has a half-life of 5 – 10 hours [93, 94, 95], and has a similar window as sildenafil [102]. The consideration in this context is mainly to educate the patient about the timing profile of each drug, so that he can adjust his social and relationship contexts accordingly.

5.4. Dose-response relationship: Dose-response relationship is an important parameter of any drug. If the effect is related to the dose, the dose escalation can be done if the initial response is not satisfying. The escalation can be prescribed by a clinician; however, it can also be done by patient after the comprehensive education about the indices of success and failure, and within the context of regular re-assessment. the dose-dependent effect appears in the available PDE5i, e.g. sildenafil (the range of dose is 25 – 100 mg) [34, 71, 102], avanafil (the range of dose is 50 to

200 mg), vardenafil (the range of dose is 5 – 20 mg) and tadalafil (in the range of 10 – 20 mg on-demand dose) [93, 94, 95].

5.5. Daily dose vs on-demand dose:

The real effect of a daily dose style is studied through various analytic approaches [18]. In comparison to placebo, the daily dosing is associated with a significant improvement in the erectile function. In comparison to the on-demand style, the daily dosing is associated with an improved erectile function. The analysis of general effects of on-demand and daily dosing regimens on the quality of erectile function revealed equal beneficial biologic effects on erection and rigidity. The use of tadalafil daily dosing regimen for non-responder to tadalafil on-demand regimen showed a significant improvement in about 50% of cases [15, 30, 103-107].

5.5.1. Rationale: The rationale of daily dosing started from many cases in which the failure of treatment was related mainly to unpreparedness. The unpreparedness represents a problem with an increased frequency of sexual intercourse per day. It also results in a loss of spontaneity, which causes discomfort to the patient and his partner too. One solution to this problem is to dissociate the treatment from the sexual intercourse. If the maximal effective plasma levels can be maintained for longer duration, rigid erection might be achieved with fewer restrictions to time.

5.5.2. Advantage: the daily dose regimen of PDE5i increases the sense of naturalness and spontaneity. It allows for frequent sexual intercourses and is also associated with an increased sense of sexual well-being and self-confidence [93, 94, 95].

5.5.3. The biologic evidence of advantage: Tadalafil is the first PDE5i molecule approved for daily dosing. Tadalafil has a dose-dependent effect, in which the erectogenic effect increases

with the increase in oral dose and plasma levels. The long-term effects of Tadalafil on the erectile tissue persists even after the cessation of the therapeutic regimen [94].

The long-term advantages of Tadalafil are related to its biologic effects on vascular and cavernosal functions. It has been shown that the chronic use of PDE5i reduces the vascular stress caused by endothelial injury associated with aging and diabetes as proved by Sildenafil [108] and Tadalafil [109]. Tadalafil also causes remodeling of vascular bed. These changes have their positive effects on the erectile function that persists after the stoppage of the daily dose [93, 94, 95].

5.5.4. The clinical evidence of advantage: At another level, the long-term effects showed significant evidence of clinical benefit. After a one-year follow-up of patients under Tadalafil daily dose regimen, the erectile function showed progressive improvement over time. More than 80% of patients improved at least one aspect of erectile function. After a two-year follow-up, this regimen showed good tolerability and the safety profile was not different from the on-demand style. Four weeks later after the cessation of therapy, further 44% of patients still got improved in at least a further aspect of the erectile function [30, 93, 94, 95].

5.6. Generic vs brand products:

Due to the large market of brand and generic manufacturers of PDE5i drugs, efficacy may be compromised when switching to generic products to lower costs. Cost can increase when considering long-term regimen or daily dose regimen. In another way, expensive drugs cause incompliance in societies with low incomes. The availability of the prescribed drug usually helps to reduce cost, increase adherence to treatment and achieve long-term efficacy as well [9, 10, 18].

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6. Considering comorbidities

6.1. Why should comorbidities be considered?

ED, age and comorbidities are factors associated to each other. Age is associated with the increased rate of ED and chronic illnesses like; diabetes [110], hypertension, dyslipidemia, metabolic syndromes [44], depression and cardiovascular dysfunctions [111, 112]. Addressing these factors in details is of critical importance in both diagnostic workup and treatment of ED [27].

The early diagnosis and treatment of atherosclerotic risk factors and the control of glycemic state will certainly reduce the progression of cavernosal endothelial damage and enhance the response to erectogenic drugs [42, 113]. Patients with impaired renal or hepatic functions affect the metabolism and the elimination of PDE5i and testosterone metabolism, making it more difficult to adjust the dose to avoid side effects and achieve acceptable outcomes.

6.2. What is the importance of cardiovascular disease considerations? [2]

6.2.1. The intimate relationship: Both conditions share similar risk factors, e.g. aging, obesity, smoking, metabolic syndrome, diabetes, hypertension, dyslipidemia and depression [42, 111]. One of the most interacting relationships with the development and course of ED is the status of cardiovascular function and pathology [114].

6.2.2. The predictive value of ED: Recent data showed that the development of ED may predict the development of CAD within the few consequent years. The explanation of this phenomenon was based on the consequent occlusion of arteries according to the artery size hypothesis [115]. So that the smaller cavernosal artery occludes first causing ED and then the larger coronary artery occludes causing CAD [66].

6.2.3. Recommendations of screening and treatment: The recommendations of Princeton Consensus Panel Guidelines have emphasized this relationship a in clinical manner [116]. The presence of either condition should prompt the clinician to consider screening for the other. [76, 117, 118].

6.2.4. Safety of PDE5i in heart diseases: Many studies showed safety of using PDE5i in properly selected patients with cardiovascular disease. However, patients with severe conditions lie in the NYHA category of II or higher and conditions with low left-side output or impaired autonomous control of blood pressure should be investigated thoroughly before institution of any ED treatment. Nitrates should not be used within 24 hours of PDE5i intake (extended to 48 hours with tadalafil) because of the synergetic hypotensive effects of both agents [114].

7. Follow-up Considerations

During the course of treatment, the clinician should consider regular monitoring of the patient. This strategy will improve the compliance to treatment and reduce adverse effects [67].

7.1. Monitoring (physician prospect)

7.1.1. Patient education: Patient education regarding the advantage and drawback of the available options of ED treatment will help him to select the most suitable one for his need. Furthermore, educating the patient about the correct and safe techniques of drug administration, e.g. injection or intra-urethral insertion, will help to reduce the rate of complications and achieve the desired outcome [11, 119].

7.1.2. Indices of success/failure: At least 6 to 8 attempts of sexual intercourse are needed to judge the response to an erectogenic agent [120]. A successful first trial is a positive predictor for the upcoming trials [119, 121]. The reassessment of the patient profile is needed before switching to another treatment modality because the improper use of a drug plays a significant role in the failure of a treatment regimen.

7.1.3. Adverse effects:

7.1.3.1. Why should the adverse effects be considered? The occurrence of adverse effects is not similar among all patients. Adverse effects are a main factor that determines compliance. Since PDE5i's adverse effects were studied extensively, the dissatisfaction of such patient should be approached by differentiating whether it is related to the drug, to the course of associated comorbidities, to other co-administered pharmacologic agents, or to a possible interaction in-between this network (93-95).

7.1.3.2. What adverse effects should be followed? Adverse effects of PDE5i can be categorized into common among all family members, or specific to each one of them. Headache, flushing, dyspepsia, and upper respiratory tract symptoms are reported with variable rates in association with all family members. Visual disturbances are more characteristic with Sildenafil and Vardenafil but not with Tadalafil or Avanafil [93, 94, 95]. Tadalafil is associated with back pain, myalgia and rarely EEG changes. Although PDE5i is rarely associated with migraine, seizures, non-arteritic ischemic optic neuritis, and reversible hearing loss, the priapism was, on the other hand, reported in few cases using PDE5i.

7.2. Tolerability (patient prospect):

Although the adverse effects may make some patients stop or change treatment, the larger percentage of patients continues a long-term treatment regimen. Tolerability is a subjective parameter and cannot be generalized or projected to other individuals. It should be added to the record of the patient and considered as a part of ED-patient response profile.

8. Social considerations:

8.1. Partner issues: When planning a regimen of treatment for ED patient, it is of particular importance to keep in mind issues related to the partner, patient occupation and the frequency of sexual act. the loss of support by the partner can play a major role in the failure of the treatment plan. Engaging the partner into the counseling sessions and decision-making increases the chances of compliance and is associated with better outcomes [16, 67].

8.2. The pattern of sexual life: the Frequency of sexual intercourse determines when and what should be prescribed for ED. This factor is one of the most important parameters to consider when someone talks about tailoring or individualizing some therapeutic plan. Frequency can be modeled into a wide range of regular and irregular patterns. However, it also can be in sporadic occasions with no regular pattern. In all these situations, the intercourse might be planned but also might not. Taking a pill for a desired effect can be a tie that limit the preparedness in most of these patterns and that can be a cause of failure or stopping treatment [91].

8.3. Cultural issues: Many cultures still consider ED as some sort of disqualification for an effective individual or a good husband, rather than a disease. ED can affect the stability of families in some cultures, while not in others. This dictates for what extent a patient asks for rapid or even urgent solutions, rather than a long-term approach, even in exchange for unclear long-term efficacy [122, 123].

9. Conclusion

Although several studies had investigated some considerations for preference and long-term adherence for oral treatment as PDE5i, however; thorough addressing of considerations for prescribing pharmacotherapy for ED treatment are still lacking in literature. This prompted us to address the considerations for prescribing pharmacotherapy for the treatment of ED. Several issues had been addressed in the current review paper such as, patients and partner expectations, etiologic considerations, performance status, safety, adverse effects, ease of administration, compliance, bad experience with previous treatment, availability, cost, satisfaction, regimen considerations and finally social factors.

10. Expert Opinion

Over the past 50 years, the treatment of ED has quickly promoted and endures to vary with new types of treatment. The intracavernosal therapy was emerged in the eighties of last century and followed by intraurethral therapy. The actual advancement in the non-surgical ED treatment was with the institution of oral PDE5i in 1998 which rapidly became the primary monotherapy. Nowadays, four PDE5i are existing in market, i.e., sildenafil, vardenafil, tadalafil and avanafil. New PDE5Is, including udenafil, and mirodenafil are presently available in several countries, and other molecules are in process.

One effective model of thinking regarding ED problem is to consider patient with ED as having a complex medical and non-medical conditions that should be targeted in assessment and modification of risk factors to properly manage ED. For example; a triad of ED, cardiovascular disease and depression has shown in multiple investigative efforts, a significant correlation and association in both directions of occurrence and recovery. Currently, several forms for ED

pharmacotherapy are accessible. With the determination of the factors that should be considered in planning of pharmacotherapy, sexual function can be successful in most of patients. Physicians should offer their patients a safe and effective drug for the disease of concern and also for the other conditions. In summary, the current mainstay treatments for ED comprise of: oral PDE5Is, VEDs, penile ICI or intraurethral suppositories, and vascular surgery or penile prosthesis. In spite of the available progress and advancement in drug development, the sustainable ideal ED treatment is still far lagging behind.

In the near future, we will witness more progress in the field of ED treatment with immerging of molecules with better safety profile as well long-term efficacy. With the appearance of new ED pharmacotherapies more concerns regarding their adverse events, efficacy, tolerability and of course their cost will continue to be important consideration in this context. In this review we have emphasized on the issues that should be considered in planning of pharmacotherapy of ED such as, patients and partner expectations, etiologic considerations, performance status, safety, adverse effects, ease of administration, compliance, bad experience with previous treatment, availability, cost, satisfaction, regimen considerations and finally social factors.

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ACCEPTED MANUSCRIPT

Article highlights box:

- Previous studies had investigated some considerations for preference and long-term adherence for oral treatment as PDE5i
- Thorough addressing of considerations for prescribing pharmacotherapy for ED treatment are still lacking in literature
- This study has addressed several issues such as, patients and partner expectations, etiologic considerations, performance status, safety, adverse effects, ease of administration, compliance, bad experience with previous treatment, availability, cost, satisfaction, regimen considerations and finally social factors.
- Despite the current advances and promising technology in drug development, the sustainable satisfactory ED treatment is still missing
- We will continue to see evolution of conservative treatment of ED until far more safe treatment options are proven by multicenter clinical trials and acknowledged by the medical community

Abbreviations:

- Erectile dysfunction (ED)
- International Index of Erectile function (IIEF)
- Low intensity extra-corporeal shockwave therapy (Li-ESWT)
- Phosphodiesterase type 5 inhibitors (PDE5i)
- Quality of life (QoL).
- Testosterone Deficiency (TD)
- Testosterone supplementation (TS)
- Intra-cavernosal injection (ICI)
- (Removed) Prostatic specific antigen (PSA)
- Sexual Encounter Profile (SEP)
- Vacuum erection device (VED)

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Figure legends:

-Figure 1: What to consider when treating ED

-Figure 2: Physician *versus* Patient and Partner Prospect

-Figure 3: Considerations to choose first line treatment for ED

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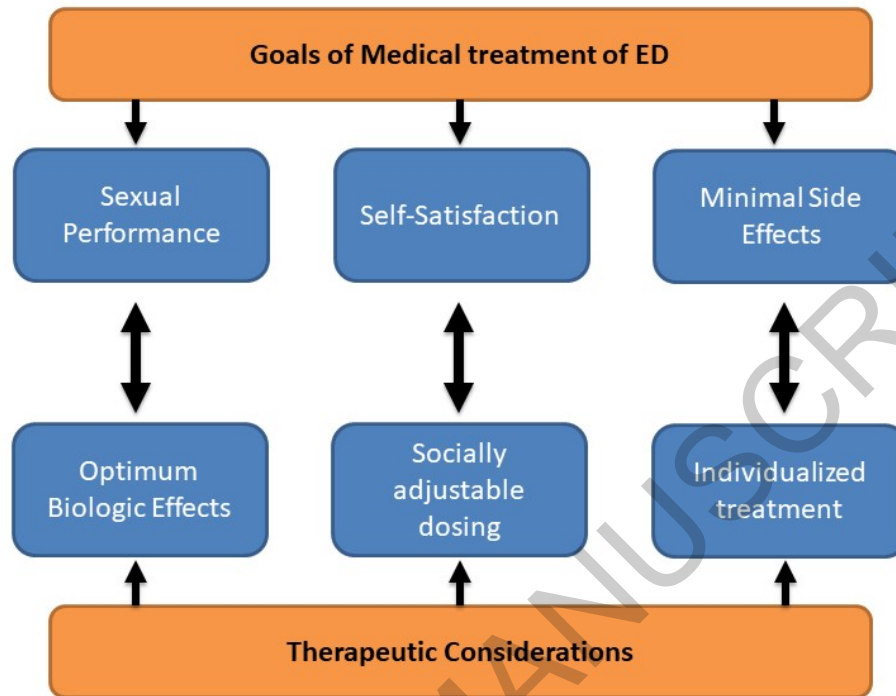


Figure 1: What to consider when treating ED?

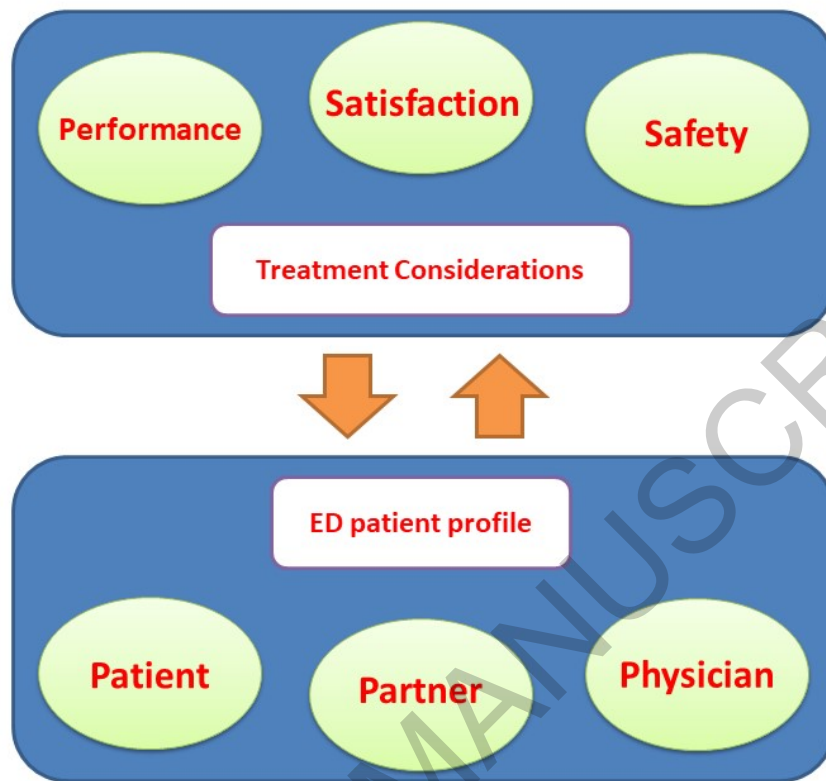


Figure 2: Physician *versus* Patient and Partner Prospect



Figure 3: Considerations to choose first line treatment for ED

Table 1: Factors that Should be Considered for Prescribing ED Pharmacotherapy
<p>1. Introduction:</p> <p>2. What should be considered when treating ED?</p> <p>2.1. Physician <i>versus</i> Patient and Partner Prospect</p> <p>2.2. Performance:</p> <p>2.2.1. <i>Biological Efficacy</i></p> <p>2.2.2. <i>Social Circumstances</i></p> <p>2.3. Therapeutic Regimen:</p> <p>2.4. Compliance:</p> <p>2.5. Previous Bad Experience:</p> <p>2.6. Adverse effects:</p> <p>2.7. Life style modification:</p> <p>3. Etiologic considerations</p> <p>3.1. Curable causes of ED:</p>

3.1.1. Testosterone Deficiency (TD)

3.1.2. Arteriogenic ED

3.1.3. Psycho-sexual issues:

3.2. Non-curable causes of ED:

4. When the PDE5i should be considered as a first line of management?

(Dynamic Step care approach – treatment planning consideration)

4.1. How could ED be treated dynamically and interactively?

4.2. What should be considered while approaching ED patients?

4.2.1. Patient preference

4.2.2. Invasiveness

4.2.3. Ease of administration

4.2.4. Re-assessment

4.2.5. Reversibility

4.2.6. Availability

4.2.7. Cost-affects compliance

4.3. Why are PDE5is most commonly used as a first line?

4.4. What kind of PDE5is should be started with?

4.5. When to bypass this approach?

4.6. What are the other lines and combination therapy?

5. Regimen considerations

5.1. Considering interval between pill intake and sexual act:

5.2. Dose adjustment with food:

5.3. Considerations regarding the duration of action:

5.3.1. Importance of duration

5.3.2. what is duration of action of each drug

5.4. Dose response relationship:

5.5. Daily dose vs on-demand dose:

5.5.1. Rationale

5.5.2. Advantage

5.5.3. The biologic evidence of advantage

5.5.4. The clinical Evidence of advantage

5.6. Generic vs brand products:

6. Considering comorbidities

6.1. Why should comorbidities be considered?

6.2. What is the importance of cardiovascular disease considerations?

6.2.1. The intimate relation

6.2.2. The predictive value of ED

6.2.3. Recommendations of screening and treatment

6.2.4. Safety of PDE5i in heart diseases

7. Follow up Considerations

7.1. Monitoring (physician prospect)

7.1.1. Patient education

7.1.2. Indices of success/failure.

7.1.3. Adverse effects

7.1.3.1. Why should the adverse effects be considered?

7.1.3.2. What adverse effects should be followed?

7.2. Tolerability (patient prospect)

8. Social considerations

8.1. Partner issues.

8.2. Pattern of Sexual life.

8.3. Cultural issues.

9. Conclusion

10. Expert Opinion

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