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Preferences and Consumptions Of Phosphodiesterase 5 Inhibitors

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ABSTRACT
Erectile dysfunction (ED) is the dominant brawl these days when seen from the sexual health point of view. Erectile dysfunction is not the disease that has only one reason;instead, many psychological, age, and lifestyle changes may lead to ED. After the development of oral PDE5I, Sildenafil by Pfizer made the treatment easier and more acceptable as before, only intracavernosal and intraurethral injections were used, which were not that acceptable by the patients. Right now,both FDA approved and non-FDA approved PDE5 inhibitors have been developed with Sildenafil, Vardenafil, Tadalafil and Avanafil in approved list and udenafil, microdenafil and lodenafil, under non-FDA class that are available commercially. ED itself is not lethal but is a prodrome of many diseases like cardiovascular problems and pulmonary hypertension. The primary objective of the study was to know about the current scenario of the market selling PDE5I and the perception and frequency of the patients or suspects buying them, and also what mentality do consumers have regarding PDE5I. After collecting sufficient knowledge about ED and PDE5 inhibitors through various PubMed articles, a questionnaire was developed and was circulated to different medical stores in the Mathura district, both rural and urban areas, the 500 complete responses were studied, and the results were calculated.
Keywords*: erectile dysfunction, Avanafil, PDE51, Sildenafil, Vardenafil, Tadalafil*

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INTRODUCTION

Erectile dysfunction is the dominant brawl these days when seen from the sexual health point of view. In one of the European study (2010), more than 30% of diagnosed men about or older than 60 years of age had been diagnosed with ED, whether moderate or severe. About 52% of a male between the age group of 40 to 70 years were found having erectile dysfunction (ED), whether moderate or severe, a study done by the Massachusetts Male Aging Study (MMAS)[1]. According to 2001–2002 National Health and Nutrition Examination in USA Survey were found flabbergasted where about 18.4% of men with 20 years of age pool were reported with ED[2]besides, 33.7% reported "sometimes able" and 36.5% to "never able" in the age pool of suspects older than 70 years of age. Due to the lack of predetermined causes, self-diagnosis is not possible in the ED. Hence it should be kept in mind that ED also appears to be the preliminary suspect of the patient being cardiovascular unhealthy. Some psychogenic problems such as poor, prior sexual experiences, low self-esteem, and relationship problems may also galvanize ED. Hence when diagnosed, all the possible reasons should be visualized. In a country like India, where men keep on hiding their intimate problems and is a part of self-esteem and social subservience, it becomes a challenging aspect to evaluate.

PATHOPHYSIOLOGY AND RISK FACTORS

Like other organ systems working cumulatively in a human body, changes and functional inability is evident as the person grows older. Aging leads to the decreased levels of testosterone synthesized through Leydig cells present in the testicle. The less rigid and frequent erection is the major age-related inability seen by aging if compared with the erectile function of a young man. These changes will surely affect a man's marital relationship. Even though they are not lethal, they may act as a forerunner of many undiagnosed diseases with hypercholesterolemia and coronary artery disease on top[3]. General possible

causes of ED may cover poor cardiovascular system, penile fracture, vasculogenic, chemical-induced or neurogenic etc[4].

DIAGNOSIS

A physician often diagnoses erectile dysfunction. As it is generally a non-self-diagnosed condition, it is the physician who should calibrate the general prodromes in suspected patients [5]. After diagnosis by a medic, the patient should be meticulous in asking the proper treatment procedure compilations because ED may be a precursor in chronic lethal diseases. The severity of symptoms, situational factors, and lifestyle are some of the questions asked; many times,questionnaires are used in the assistance of both diagnosis and treatment plan compilations for the patients[6].

TREATMENT

Since the increase of the allopathic era, many treatments are made for ED patients; yohimbine is counted as the former drug of choice. Prostaglandin E-1 analog Alprostadil has the highest efficacy in therapy with about more than 70% of potency. Still, the demerit is that it may only be administered through intraurethral or intracavernosal, which makes patient slightly to the ignoring site of acceptance because oral dosage forms are the only psychologic accepted drugs in the population [7]. With the development of phosphodiesterase-5 inhibitors, the treatment now has become more acceptable as it is given orally and has the same efficacy but some negligible side effects. Although, PDE5I shows limitations when delivered to the patients with organic nitrates taking for the treatment of angina. However, prescribing with oral medications, the physician should also discuss the surgical options as well, like intracavernosal and intraurethral therapies, the patient should also make aware of the surgical prosthesis penile implantation. Eventually, the approach is to develop the patient's quality of life by improvising sexual life and minimizing the other lethal risks like metabolic and cardiac malfunctions. Change in lifestyle is also recommended; this includes a healthy diet plan, increased physical activity, and weight loss, even the consumption of alcohol or tobacco is advised to avoid diminishing the risk of other correlated disease risk factors. In addition to this,the treatment of hyperlipidemia, diabetes, and other endocrine-related hormonal imbalance may lead to improved erectile function[8].

SILDENAFIL

Sildenafil is marked as the oldest PDE5 inhibitor to come in prescriptions; it was approved forED in 1998. As mentioned, it was a potent orally given selective inhibitor of cGMP-specific PDE5[9].Phosphodiesterase type 5 (PDE5) leads to the degradation of cyclic guanosine monophosphate (cGMP); pharmacologically, the result is seen by the smooth muscle relaxation and vasodilation induced by nitric oxide[10]. Sildenafil is found to be quick in the onset of action with a time of about 30 minutes of the dose given; however, it is generally advised to wait for 1 hour before intercourse for the maximum benefit of the drug. Available duration is found to be 4-6 hours with a max duration of up to 12 hours[11]. When it comes to the dosage form, three major dosages are available in the market (25, 50, and 100 mg). The dose may be increase or decrease based on drug tolerance and efficiency[12]. Side effects are usually negligible and are mild if seen, which may include flushing (induced due to vasodilation), headache, dyspepsia, rhinitis [9,13]. The dose is generally contraindicated with patients consuming organic nitrates for the angina treatment. Sildenafil has now been known to be very useful in minimizing the prodromes of pulmonary arterial hypertension due to is vasodilatory actions[14].The clearance level of Sildenafil inside the body is affected when the suspect is having any of the hepatic conditions like hepatic cirrhosis, elevated hepatic pressure, or hepatic congestion [15]. Even though the consumption of Sildenafil inducing hepatotoxicity is rare, in the last decade, some cases have still been reported [16].

Drug-Drug Interaction

Hemodynamic effects are well known when Sildenafil interacts with nitrates; this results in decreasing of supine pressure to about 8.4/5.5 mm Hg, although the impact on heart rate is reported to be negligible. Hypotensive effects are found to increase when Sildenafil is administered along with amlodipine (5 or 10 mg) and β-blocker like doxazosin(4mg); hence beta-blockers are generally avoided [17]. No interactive effects have been reported with alcohol, aspirin, or warfarin.

TADALAFIL

This more potent PDE5 inhibitor was known to launch in 2003. It is the 3rd drug of its kind of phosphodiesterase inhibitor category. When compared with Sildenafil, Tadalafil is found to have a much low onset of action of about 20 minutes as reported and has the maximum duration of action of 72 hours. Reports showed that about 52% of patients had successful intercourse after dose consumption 30 minutes prior [18]. Its long elimination half-life of about 18 hours makes it unique of its kind[19]. Dosage concentration is also comparatively low, with 10 mg to be given primarily; on-demand 20mg dose may also be administered. Reported mild side effects may include dyspepsia, backpain, rhinitis, and headache, 2.1% is the noted discontinuation rate of Tadalafil [20]. FDA counts Tadalafil as a drug with low solubility and high permeability (according to its biopharmaceutics classification system) [21,22]. Its oral

absorption is rapid, with about 2 hours to reach C_{max}. Although 100% of bioavailability is a matter of debate, atleast 36% of the dose is bioavailable when taken orally [22]. It has a 60 to 70 L of V_{ss}/F value with some variability according to individual [18,22]. The V_d is found to be dependent on bodyweight, an increase in 10 kg bodyweight results in a rise in V_{ss}/F value to 6.3%. Tadalafil, after metabolism forms catechol metabolite, the metabolism takes place by enzyme CYP34A (a hepatic enzyme). Methylcatechol glucuronide is the ultimate metabolite, which is found to be no pharmacological action[23]. A study on CYP34A inhibitors gave the metabolic pathway of Tadalafil[24]. 75% of Tadalafil is excreted through feces and about 25% through urine. After tedious studies on more than 4000 patients, it was found that Tadalafil is also responsible for changing the blood pressure; hence, prescribing of Tadalafil to the patients with cardiovascular disease is generally avoided [24].

Drug-Drug Interaction

Being a vasodilator, Tadalafil is found to decrease the supine BP to 1.6/0.8 mm Hg; however, no change in heart rate was observed. Many reports validate the contraindication of Tadalafil with organic nitrates like other PDE5 inhibitors; it shows a synergistic decrease in blood pressure [17,25,26]. Potentiation of hypotensive effects of Tadalafil is well reported when administered with enalapril, amlodipine, metoprolol, or bendrofluazide. Tadalafil is found to interact with alcohol as it decreases the diastolic bp comparatively more (12 mm Hg) if the alcohol content is more than 0.7mg/kg. It is also indicated to interact with β-blocker like tamsulosin because of its enhanced effects with beta-blockers. No further interactions have up to now been reported with warfarin or aspirin[27].

VARDENAFIL

Vardenafil (approved in 2003), the congener of Sildenafil, has a similar type of action, with the shortest onset of action of about 10 minutes, but 30-60 minutes is recommended before the intercourse. It has a 30-120 min peak level and $t_{1/2}$ of about 4 hours. Contraindications and side effects are similar to the Sildenafil. It is generally administered as film-coated tablets with 5,10 and 20 mg dosage forms, 10 mg form is generally recommended as starting dose.Like Tadalafil, Vardenafil is also found to be a drug having low solubility and high permeability [12]. Studies showed that the $C_{max}$of the drug was found to about 3 hours. The absolute bioavailability is approx. 15% [25]. Distribution involves boundation of drug to 80% in albumin and 11% to the α1-acid glycoprotein. An investigation was also done by administrating Vardenafil to the intravenous route there the V_{ss}/f value was found to be 208L; it is concluded that 0.00018% of the dose appears in semen [28]. Vardenafil is metabolized to about 14 metabolites. Metabolite M1 (N-diethyl vardenafil) is known as a major, and M4 and M5 (including their glucuronides) are termed as minor ones. CYP3A4 is known to mediate the process of metabolism. In the case of Vardenafil, metabolites are found to be active in showing pharmacological actions, with M1 to be 28% potent as Vardenafil and M4 and M5 to be 5.6 and 4.9, respectively [28]. Elimination takes place through feces and urine with 95% and 2-6%, respectively, about 1% is excreted unchanged through urine. When administered through I/V,56 L/h total body clearance was identified, and elimination half-life was found to be about 4 to 5 hours. Studies documented that it is a drug having a high hepatic extraction ratio [28,29].

Drug-Drug Interaction

The drug is found to lowering the supine pressure to about7/8 mm Hg and is found to increase heart rate to about 4BPM. As Vardenafil may catalyze the hypotensive and vasodilatory actions of nitrates and NO payers hence it is generally avoided to prescribe to patients receiving these therapies. The same is with β-blockers like terazosin (10 mg) and tamsulosin (0.4 mg), as Vardenafil is found to cause hypotension in some patients. A hypotensive effect of about 6/5 mm Hg in supine BP may also be observed when given with nifedipine (30 mg). No drug interaction was observed in the presence of glyburide, aspirin, and warfarin [28].

AVANAFIL

This latest developed PDE5 inhibitor, approved in 2012 by the international pharmaceutical regulating agencies in the United States and Europe, is capable of the more potent treatment of ED, either mild or severe. Even though it is well-tolerated medicine, still 14% of patients reported side-effects like headache and flushing in clinical trials[11]. The drug had passed several clinical trials on patients with varying ED. 30 minutes before the intercourse, 100 mg of Avanafil was given. A clinical meta-analysis of Avanafil was done in which test on 1379 male suspects was done, out of which 605 were administered with placebo. The ratio, when compared, was found to be 2.51 (100mg avanafil) and 2.87 (200mg avanafil) [30]. The metabolism of Avanafil is similar to other PDE5 inhibitors; it is also metabolized through hepatic enzyme CYP3A4. Primary formed metabolites include M4 and M16, but only M4 pharmacological activity M16 is generally an inactive metabolite[31]. The half-life is found to be longer than all the PDE5 inhibitors but is only one third when compared with Tadalafil.

MATERIAL AND METHODS

SUBJECTS AND METHODS:

Study design

It was a questionnaire-based study.

Study setting

The study/survey was conducted in and with the help of the various medical stores of the Mathura district.

Study-participants

Patients with ED were the primary participants to be studied.

Study-procedure

Medical stores in the Mathura district were contacted in the first week of February 2020; they were provided with the questionnaire and requested to get them filled by the patients taking PDE5 inhibitors. The questionnaire was well discussed with the pharmacists to avoid any confusion regarding any question as patients may not aware of some of the problems.

Statistical-analysis

The returned questionnaires were checked for completeness of data. The data obtained from the completed questionnaires were analyzed in the computer by using Graph Pad Prism Software Version 6.0. Descriptive data were expressed as percentages and frequency.

RESULTS

Demographic characters of the study

In this demographic study, the information we got from consumers who have taken phosphodiesterase 5 inhibitors, with the help of 500 forms, which we got filled gives the data that is mentioned below in the table.

Demographic factors	Categories	Total n (%)
Age	30-40 years	73 (14.6)
	40-50	237 (47.4)
	>50	190 (38)
Marital status	Married	438(87.6)
	Unmarried	42 (8.4)
	Divorced/Separated	20(4)
Employment	Employed	383 (76.6)
	Unemployed	117(23.4)
Literacy status	Literate	412(82.4)
	Illiterate	88(17.6)
Educational qualification	$<10^{th}$	88(17.6)
	$10\text{-}12^{th}$	60(12)
	Degree holders	352(70.4)
Chronic medical condition	Yes	353(70.6)
	No	147(29.4)
Number of pharmacy visit	One time in a month	373(74.6)
	More than 2 times in a month	127(25.4)

Table 1: Demographic characters of the study data

Customers frequency and perception about phosphodiesterase—inhibitors

In this study, the information we got from consumers who have taken Phosphodiesterase-5-inhibitors choose more than one option in the questionnaire, so the calculation varies according to their choices (considered all selections in the calculation if marked more than one option). Consumer's frequency and perception of PDE5I are presented in Figure 1A. 108/500 (21.6%) of the study population were taking PDE5I rarely, 362/500 (72.4%) PDE5I occasionally, and 30/500 (6%) practiced PDE5I weekly. When asked about the source of information for practicing PDE5I, consumers stated that they primarily took advice from family, friends, and neighbors 14.4% (72/500), some sought input from a pharmacist 30.6% (153/500), some came to know about the medication via previous prescription 52.6% (263/500), and very few gained about the medicine from drug directory 14.4% (12/500) respectively Figure 1B. Further, we analyze the subject's choice of medication. It was found that 322/500 (64.4%) patients were buying Sildenafil, 160/500 (32%) Tadalafil, and 18/500 (3.6%) were taking Avanafil Figure 1C. When came

about the knowledge of the medication, the results gave the data that 272/500 (54.4%) patients knew about the medicine, and the remaining, i.e., 228/500 (45.6%), were unaware about the medicine Figure 1D.

Figure 2 depicts the marked adverse effects with the particular PDE5I; many suspects marked more than one side effects from the option given; also, some forms shown that the suspects see no side effects. The significant side-effects include headache and flushing 146/322 by Sildenafil, 08/160 by Tadalafil and 13/18 by Avanafil, then comes the Indigestion suspects says 282/322 by Sildenafil, 16/160 by Tadalafil and 10/18 by Avanafil respectively found some kind of indigestion, back pain was also a common side-effect found the data says, 290/322 by Sildenafil,48/160 by Tadalafil and 16/18 by Avanafil, also PDE5I were found to cause loss of appetite it was found 278/322 suspects were having loss of appetite by consuming Sildenafil, 58/160 by Tadalafil and 13/18 by Avanafil. Only 32/322, 102/160, and 02/18 suspects reported not to felt any side-effects by consuming Sildenafil, Tadalafil, and Avanafil, respectively.

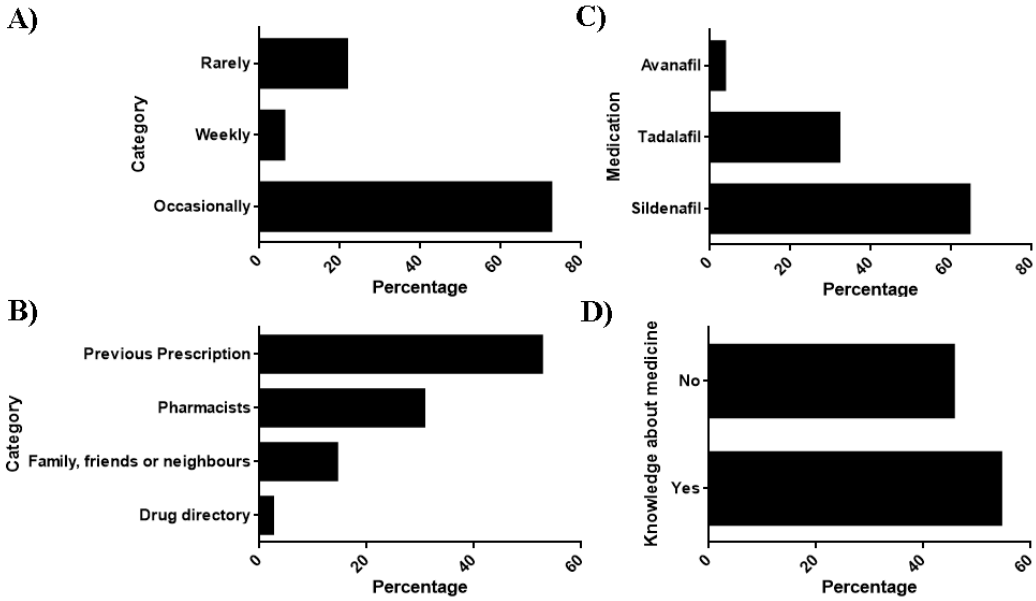

Figure 1: Frequency and perception about PDE5I

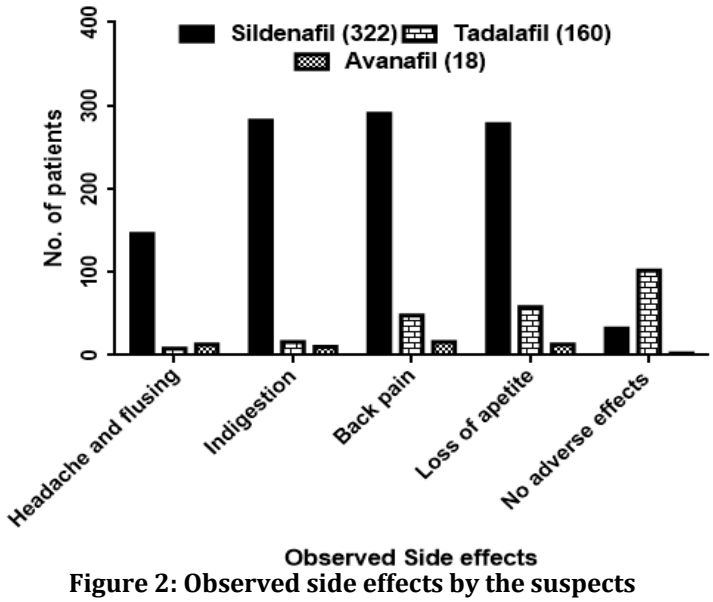

Figure 2: Observed side effects by the suspects

DISCUSSION

ED is the ubiquitous men intimate disease, India being one of the capitals of patients suffering from ED, forms the vast market of PDE5 inhibitors, including Sildenafil, on top consumption followed by Tadalafil and Avanafil respectively. Due to a lack of predetermined causes, self-diagnosis is not every time possible; hence the problem keeps on shifting towards the severe side by time. In a country like India, where men

keep on hiding their intimate problems and is a part of self-esteem and social subservience, it becomes a challenging aspect to diagnose or evaluate.

Not or less acceptance of surgical methods and intracavernosal and intraurethral injections, the Indian populations mostly depend on oral PDE5 inhibitors. Our survey states that out of 500 studied patients, 64% were buying Sildenafil, and 32% & 3.6% were the consumers of Tadalafil and Avanafil, respectively (Figure 1-c). As more accepted, the oral PDE5 inhibitors were found to show some side-effects like headache & flushing, indigestion, backpain, and loss of appetite (Figure2- By survey).

When comes to the pathophysiology of ED, it is observed that, likewise, other organs of the body, the penile vascular functions for erection also decrease; this may be connected to age affected lowering of testosterone produced in Leydig cells of the testis. But it cannot be denied that some patient was not of that much age; hence lifestyle variations, penile fracture, & hereditary factors may also mark in causing erectile dysfunction[4].Even though ED is not lethal but may act as a forerunner of many diseases like hypercholesterolemia& coronary artery disease.

Quest of PDE5 inhibitors in stimulating penis erection was accidental; it was observed as a side effect when the investigation was being done in the treatment of angina and hypertension. Both FDA approved, and non-FDA approved PDE5 inhibitors have now been developed with Sildenafil, Vardenafil, Tadalafil, and Avanafil in approved list and Udenafil, Microdenafil and Lodenafil come under the non-FDA class that is available commercially.

Sildenafil is marked as the oldest PDE5 inhibitor to come in prescriptions; it was approved for ED in 1998. As mentioned, it was a potent orally given selective inhibitor of cGMP-specific PDE5 [9]. The mechanism of action is by the inhibition of the enzyme phosphodiesterase type 5 (PDE5), which leads to the degradation of cyclic guanosine monophosphate (cGMP), pharmacologically the result is seen by the smooth muscle relaxation and vasodilation induced by nitric oxide[10].Hypotensive effects are found to increase when Sildenafil is administered along with amlodipine (5 or 10 mg) and β-blocker like doxazosin(4mg); hence beta-blockers are generally avoided[17]. No interactive effects have been reported with alcohol, aspirin, or warfarin.

When compared with Sildenafil, Tadalafil is found to have a much low onset of action of about 20 minutes as reported and has the maximum duration of action of 72 hours. Reports mentioned that about 52% of patients had successful intercourse after dose consumption 30 minutes prior [18]. Its long elimination half-life of about 18 hours makes it unique of its kind[19]. Being a vasodilator, Tadalafil is found to decrease the supine BP to 1.6/0.8 mm Hg. However, no change in heart rate was observed. Many reports shown the contraindication of Tadalafil with organic nitrates like other PDE5 inhibitors; it offers a synergistic decrease in blood pressure [17,25,26]. No further interactions of Tadalafil have up to now been reported with warfarin or aspirin.

The Avanafil latest developed PDE5 inhibitor approved in 2012 by the international pharmaceutical regulating agencies in the United States and Europe is capable of the more potent treatment of ED, either mild or severe. Even though it is well-tolerated medicine still 14% patients reported of side-effects like headache and flushing in clinical trials [11]. The drug had passed several clinical trials on patients with varying ED. 30 minutes before the intercourse, 100 mg of Avanafil was given. A clinical meta-analysis of Avanafil was done in which test on 1379 male suspects was done, out of which 605 were administered with placebo. The ratio, when compared, was found to be 2.51 (100mg avanafil) and 2.87 (200mg avanafil) [30].

CONCLUSION

Five hundred subjects were taken to participate in the study. Demographic characteristics such as age, marital status, employment status, literacy status, and educational level were represented in Table 1. Out of 500 respondents, 82.4% (412/500) were literate, 87.6% (438/500) respondents were married, and 76.6% (383/500) were employed. 70.6% (353/500) subjects had chronic diseases, and 74.6% (373/500) subjects visited the pharmacy at least once in a month during the study period. Oral PDE5I are found to be very much efficient in treating the ED in the Indian market; even though they have some side-effects like headache and flushing, loss of appetite, indigestion, and back pain, they are very much accepted then the intracavernosal and intraurethral injections.

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