Non-invasive management of primary phosphodiesterase type 5 inhibitor failure in patients with erectile dysfunction

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***Abstract*:** Phosphodiesterase type 5 inhibitors (PDE5-i) have become first line therapy for the treatment of erectile dysfunction. Most initial prescriptions for PDE5-i are by primary care practitioners. Urologists must now routinely manage the patient who has failed initial therapy with PDE5-i. Lifestyle modifications can be of benefit to patients. Patient education and optimization of the PDE5-i can result in a successful response. Interestingly, there are reports of up to 60% salvage after changing the PDE5-i utilized. Daily PDE5-i have shown benefit, and treatment of hypogonadism can enhance response to PDE5-i. We review the management of PDE5-i failures with emphasis on noninvasive approaches to gaining improved erectile response to these medications. An algorithm based on the reviewed strategies is proposed to guide clinicians in the treatment of erectile dysfunction.

***Keywords*:** erectile dysfunction, phosphodiesterase inhibitor, treatment failure

Introduction

Phosphodiesterase type-5 inhibitors (PDE5-i) have become first-line treatments for men presenting with erectile dysfunction (ED). Most initial prescriptions are now by primary care practitioners [McMahon *et al*. 2006]. However, up to 35% of these patients fail to respond and medication represcription rates drop to 30% when followed for 12 months. The American Urologic Association (AUA) guidelines for management of erectile dysfunction suggest PDE5-i should be offered as first-line therapy for erectile dysfunction unless contraindications exist. Further-more, the guidelines state other treatment options should be evaluated for invasiveness and risk, balanced with the potential likelihood for efficacy, and applied in a stepwise fashion. This can leave the urologist and patient alike wondering what is truly the next best option. Some patients may never present for discussion of further treatment due to a lack of knowledge of alternative options or concern regarding the invasiveness of other treatments. Fortunately, other noninvasive treatment options exist to facilitate response to PDE5-i.

Reasons proposed for failure of initial PDE5-i treatment include worsening endothelial dysfunction, severe baseline erectile dysfunction, veno-occlusive dysfunction, nervous input injury, or tachyphylaxis [McMahon *et al*. 2006]. Unrecognized hypogonadism and inadequate patient education have been found to compromise patient response to PDE5-i as well. Psychosocial factors are known to affect erectile function and may not be overcome with PDE5-i treatment. These causes of failure are important to understand, as current practice in diagnosing and treating erectile dysfunction begins with PDE5-i. Further work-up is then applied only for patients who fail initial therapy. While this is likely to be a cost effective approach, patients may become discouraged when their initial response is sub-par. We review the management of PDE5-i failures with emphasis on noninvasive approaches to gaining improved erectile response to these medications.

PDE5-inhibitors

All currently available PDE5-i function through a similar mechanism of action. Each PDE5-i has a heterocyclic nitrogen-containing double ring system. PDE5-i prevent breakdown of cyclic guanosine monophosphate (cGMP) allowing smooth muscle relaxation and penile erection to remain. It is important that patients realize that without

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sexual stimulation, PDE5-i are ineffective and do not cause erection. No direct head to head trials comparing these medications exist.

Sildenafil is the most extensively studied PDE5-i. The time to maximal plasma concentration is 0.8 h and onset of action is between 15 and 60 min. Half life is 3–5 h. Vardenafil has a time to onset similar to sildenafil. Peak plasma concentration occurs at 0.7 h and the half life is 4–5 h. Tadalafil has a longer time to peak concentration at 2 h and a longer half life of 17.5 h. Onset of action is reported to occur as early as 15 min, but it is likely to require longer for most patients [Carson, 2007]. Sildenafil is the most affected by consumption with a fatty meal, and this reduces absorption. Vardenafil shows reduced absorption as well, but this does not appear to be an issue with tadalafil.

PDE5-i failures

Lifestyle modification

Failure of PDE5-i treatment occurs in 30–40% of patients and represcription rates drop to 30% when followed for a year [Carson, 2007; McMahon *et al*. 2006]. These data suggest that there are a substantial number of patients who require more detailed and extensive strategies to facilitate response to PDE5-i. Such strategies are likely to be underutilized by primary care physicians, and possibly under-recognized as beneficial in urologic practices. Many options exist to improve patient response to PDE5-i, and most require implementation of 'personalized medicine'.

A study reviewing risk factors for poor response to sildenafil in Korean men revealed a low pretreatment erectile function domain score as the most predictive of treatment failure. This was closely followed by hypogonadism and current smoking on multivariate analysis [Park *et al*. 2005]. Obesity, smoking, and sedentary lifestyle have all been shown to increase rates of erectile dysfunction [Bacon *et al*. 2003; Derby *et al*. 2000; Feldman *et al*. 2000; Mannino *et al*. 1994]. This knowledge offers the urologist a unique opportunity to provide a man with erectile dysfunction motivation to change these lifestyle factors. Esposito *et al*. [2004] performed a randomized controlled study on men with a body mass index (BMI) greater than 30 and international index of erectile function (IIEF) score of 21 or less. No man had diagnosed diabetes, hypertension, or hyperlipidemia. Men were 35–55 years in age. Men in the intervention arm were given detailed advice on how to reduce body weight by more than 10%, including psychological and behavioral counseling, monthly nutritionist visits with individualized recommendations, and guidance on increasing physical activity. Men in the control arm received oral and written information on healthy food choices and exercise. After 2 years, men in the intervention arm had a significantly greater decrease in BMI and significantly greater increase in physical activity. In addition, IIEF increased from a mean of 13.9 to 17 ($p < 0.001$) in the control arm with 17 men of 55 reporting an IIEF score of 22 or greater. In the control arm, there was no significant change in IIEF (13.5–13.6, $p = 0.89$) but three of 55 patients obtained an IIEF score of 22 or greater. In multivariate analysis, changes in BMI and physical activity were both independently associated with improvement in IIEF. As previously noted, this information provides the treating urologist with an opportunity to promote a healthy lifestyle while reaching the endpoint of improved erectile function.

In addition to smoking cessation, weight loss, and increased physical activity, pelvic floor muscle exercises have shown benefit in returning erectile function [Dorey *et al*. 2005]. Fifty-five men with erectile dysfunction of >6 months duration were randomized. Twenty-eight underwent initial pelvic floor exercises directed by a physiotherapist and 27 composed the control arm. After 3 months, no improvement was seen in the control group compared with significant improvement ($p < 0.001$) in the pelvic floor exercise group. The control group then underwent pelvic floor muscle training. A significant improvement was seen at the 6 month assessment. Overall, including both groups, 40% of men regained normal erectile function and another 35% showed improvement. Median IIEF score was nine pre-therapy and 22 post-therapy for the initial intervention group. Median IIEF score was seven pre-treatment and 20 post-treatment in the initial control group. Unfortunately, further characteristics of included patients were not included in the article and follow-up was not reported past 9 months.

Optimization of PDE5-i treatment

Pelvic floor exercises, smoking cessation, increasing physical activity, and weight loss can be useful

in many patients. Patient compliance, especially long term, may limit the beneficial effects witnessed in studies utilizing intensive counseling. Even with patient compliance, some patients will progress to needing further therapies as they age. The American Urological Association (AUA) has recommended that patients who fail a PDE5-i should be evaluated to determine whether the trial was adequate prior to proceeding with other therapies. Many men may have tried a sample pack of three tablets or had inadequate instruction from the prescribing physician. Other men may have misunderstood or forgotten what was given as instruction. Regardless of the reason for inadequate response, the urologist should focus on ensuring men have attempted a proper trial of a PDE5-i.

McCullough *et al.* [2002] evaluated six double blind, placebo controlled, flexible dose studies to evaluate the number of attempts with sildenafil necessary to achieve intercourse success. Over 1200 men were included. Overall 54% and 64% had success on the first and second trial respectively. The cumulative probability of achieving success reached a plateau of 86% around the eighth attempt. This plateau was irrespective of the severity of erectile dysfunction, however patients with severe ED had a lower success rate. This group continued with a retrospective review of 137 consecutive men who failed initial attempts with sildenafil. Eighty-three percent were available with complete follow-up. Over half reported a maximal initial dose of 50 mg or fewer than five attempts at use. Only a third recalled the primary care physician discussing the affect of food or alcohol consumption with sildenafil. Of the 114 men, 23% elected no further therapy and 2.6% had a contraindication. Patients were educated on the need for sexual stimulation, timing of when to take the medication, food and alcohol consumption, and the need for multiple attempts after dose titration. Eighty-five patients were re-educated and 11 elected no re-challenge due to side effects. Through this educational process, 54% were able to become responders with proper dose escalation and numbers of attempts.

A multicenter prospective study of patients recruited through local advertisements for failure or dissatisfaction with initial attempts of sildenafil found over half of men had received sildenafil from a nonmedical source [Gruenwald *et al.* 2006]. These patients were excluded from further evaluation. For the remaining patients, comprehensive instruction in both written and oral format was given to the 346 patients. Patients were re-challenged with sildenafil on-demand. Three visits composed the intervention period, each 1 month apart. The overall success rate was 39% in an intent-to-treat analysis. This included 146 patients who dropped out as failures. One-third of patients required six to eight doses to achieve success. When IIEF was evaluated between visits one and two and visits two and three, the greatest increase was seen between the initial two visits.

Optimization has also been shown to be effective with tadalafil and vardenafil [Hatzimouratidis *et al.* 2006]. Two groups of patients were evaluated with each consisting of 100 patients who had had previous unsuccessful treatment with vardenafil or tadalafil. Each group underwent three phases. Phase 1 consisted of identification of inappropriate medication usage and included written information on proper use of the drug based on labeling information for tadalafil or vardenafil. This included taking tadalafil at least 30 min prior to sexual intercourse and taking vardenafil at least 25 min before sexual intercourse and avoiding fatty meals. Patients who had used medication inappropriately were asked to attempt four trials prior to proceeding to phase 2. Patients with insufficient response entered phase 2 consisting of education to take tadalafil 2 h prior to intercourse and only take vardenafil in a fasting state. In the tadalafil group, there was inappropriate medication usage by 32 patients, most having had fewer than four attempts. Of these patients, 43% responded with education and dose escalation. Eighty-six patients entered into phase 2, and after allowing greater time prior to attempting sexual intercourse 32 (37%) responded. In the vardenafil group, 38 patients were recognized to have had inappropriate usage, all of whom had had fewer than four doses. After dose titration and education, 32% responded successfully. Eighty-eight patients entered phase 2, with 22 (25%) responding to usage with a fasting state.

Each of these studies reveals a substantial number of patients who respond after education and dose escalation to maximal recommended doses of sildenafil, vardenafil, or tadalafil. Urologists occasionally hear a patient comment that higher doses of PDE5-i allow success. One study evaluated this phenomenon [McMahon, 2002]. Thirteen of 54 (24%) responded at a

maximal dose of 200 mg. However, four of 13 (31%) responders refused to continue treatment due to adverse events and 63% of all patients experienced side effects.

Rescue with a different PDE5-i

In the PROVEN (patient response to vardenafil in sildenafil nonresponders) study a 61% salvage rate was found for patients previously failing sildenafil by self-reported history [Carson *et al*. 2004]. Patients verified that they made at least six attempts with sildenafil according to the package insert, at least one at 100 mg, and failure of four of those six attempts. The intent-to-treat analysis included 229 patients in the vardenafil arm and 225 in the placebo arm. After 12 weeks of treatment, 61% of men in the vardenafil arm reported improved erections, and 31% achieved an erectile function domain score consistent with a normal score (>25). Erectile function domain scores for penetration doubled and for successful intercourse quadrupled over baseline. In the placebo group, 15% of men reported improved erections and 6% had normal erectile function. However patients were not re-challenged with sildenafil after further education and prior to enrollment into the study.

Brisson *et al*. [2006] also evaluated the response of sildenafil nonresponders when re-challenged with vardenafil. In this observational study, patients were considered sildenafil nonresponders only after attempting four trials at the 100 mg dose. Of 327 men presenting complaining of inadequate sildenafil response, 59 went on to attempt vardenafil. Only 12% (seven of 59) noted a significant response with vardenafil. Those most likely to respond were significantly more likely to have no abnormality on doppler ultrasonography after intracavernous pharmacologic injection, take cholesterol medication, and had a greater incidence of Peyronie's disease.

A substantial difference in response is observed between the two trials presented. While response to a different PDE5-i may only be 12%, patients may choose this trial prior to other options due to the ease of administration and its noninvasive nature.

Daily PDE5-i treatment

The third phase of the previously mentioned study by Hatzimouratidis *et al*. [2006] utilized vardenafil or tadalafil in a daily regimen. Tadalafil was given at 20 mg every other morning and vardenafil at 20 mg every day 3 h after a meal, each given for 2 weeks. In the tadalafil group, 34 of 54 phase 2 nonresponders agreed to participate, and six patients (17%) responded. Of 66 patients failing phase 2 in the vardenafil group, 32 participated in daily dosing. Twelve patients (37%) of those participating responded to daily dosing.

In a second study, patients trialed 20 mg of tadalafil on demand for 4 weeks followed by 4 weeks off therapy [McMahon, 2004]. Stringent inclusion criteria included attempting 20 mg of tadalafil according to the manufacturer's prescribing recommendations on at least six separate occasions, with at least two attempts at sexual intercourse in the following 24 h on 67% of these occasions. One attempt had to be within 8–12 h of dosing. An adequate trial of sildenafil had also been attempted in 96 of the 112 (86%) men. After the 4 week treatment free period, daily 10 mg tadalafil was initiated. This was increased to 20 mg daily after 4 more weeks for patients unsatisfied with response to 10 mg daily. Twelve weeks of daily treatment led to an increase in erectile function domain scores on IIEF from 10.3 at baseline and 14.9 with on-demand tadalafil, to 23.1 and 22.4 with daily 10 mg or 20 mg tadalafil respectively. Both daily dosing schedules were significant when compared with baseline and on-demand tadalafil. With daily 10 mg (41%) and 20 mg (32%) dosing there was also a significant increase in those returning to a normal erectile function domain.

Other studies have confirmed the benefit of daily PDE5-i dosing, although not necessarily in patients previously failing on-demand therapy. Using a randomized, double-blind, placebo controlled, parallel-group, 12-week daily dosing schedule comparing placebo with 5 mg and 10 mg daily tadalafil, Porst *et al*. [2006] found 84% benefit for both treatment groups compared with 28% in the placebo arm. Olsson *et al*. [2000] found daily dosing with sildenafil to significantly ($p < 0.001$) improve frequency, hardness, and duration of erections when compared with placebo.

Daily PDE5-i therapy is proposed to activate endothelial nitric oxide synthase, enhance systemic vasodilation response, and have favorable effects to counter systemic endothelial dysfunction [Bella *et al*. 2007]. Increased usage via daily PDE5-i has led some to become concerned that

tachyphylaxis may develop. El-Galley *et al.* [2001] proposed that tachyphylaxis could occur based on the results of a survey which questioned patients 2 years after beginning sildenafil treatment and revealed that 50% of patients stopped using sildenafil due to lack of efficacy and another 37% had increased the dosage. This study was unable to determine whether the decreased efficacy over time was due to disease progression or tachyphylaxis. Currently, it is unclear if tachyphylaxis develops with daily PDE5-i use and several animal studies have suggested this is not the case [Bella *et al.* 2007; McMahon, 2004].

Hypogonadism and PDE5-i failure

Based on the observation that a low serum testosterone was associated with impaired cavernous vasodilation, Shabsigh *et al.* [2008] hypothesized that hypogonadal patients failing sildenafil may be salvaged with the addition of testosterone replacement. Seventy-five patients with a morning total serum testosterone of 400 ng/dl or less on two occasions 14 days apart and nonreponsive to 100 mg sildenafil on-demand therapy were randomized to adjunctive 1% testosterone gel or placebo daily. Response was judged using questions 3 and 4 of the IIEF with a numeric response of 4 or 5 on both indicating success. After 4 weeks of therapy, a significant difference was noted with 51% of treatment patients responding compared with 27% of patients receiving placebo gel. Overall significance was no longer present by week 8, however the number of responders was higher at each interval in the treatment arm. The authors proposed the small sample size as likely leading to loss of significance between the groups. In men with hypogonadism, testosterone replacement therapy may facilitate improved erectile functional response to PDE5-i.

Adjunctive measures

Pioglitazone as an adjunctive treatment has been compared in combination with sildenafil against sildenafil alone [Gholamine *et al.* 2008]. Thirty-eight men who had failed four trials of sildenafil were randomized to 9 weeks of pioglitazone 30 mg daily or placebo. Pioglitazone significantly ($p < 0.05$) improved the sildenafil responsiveness at the 9 week endpoint, increasing mean IIEF score from 13.3 to 17.6 compared with no change in the placebo group. Total cholesterol also showed a significant decrease in the treatment group.

De Rose *et al.* [2002] evaluated 28 patients in a randomized, prospective, placebo controlled trial of the addition of 4 mg doxazosin daily versus placebo in patients refractory to sildenafil. After 60 days of treatment, 11 of 14 (79%) of doxazosin treated patients reported significant improvements in the IIEF when re-challenged with sildenafil. This compared favorably with only one of 14 (7%) in the placebo group noting improvement ($p < 0.0016$). During office evaluations, no significant changes were noted in blood pressure, and only one new adverse event was noted, consisting of heartburn in one patient.

PT-141 (bremelanotide) is a melanocortin analog and has been shown in preliminary studies to have a beneficial effect on erectile function. Recently a publication by Safarinejad and Hosseini [2008] showed benefit of bremelanotide in sildenafil failures. Patients referred to a single clinic were given written instructions on appropriate sildenafil use with regards to food, alcohol, timing and number of attempts that may be necessary for response. Patients were instructed to attempt 12 trials at home with 11 of these doses at 100 mg before treatment was considered to have failed. Of 448 patients, only 13% responded to re-education and these attempts. Nonresponders therefore consisted of 388 men but only 304 patients completed the trial after exclusions and dropouts. Significant improvement was noted in the bremelanotide group compared with the placebo group, with 33.5% and 8.5% responding to treatment with the ability to attain and maintain an erection strong enough for intercourse ($p = 0.03$) on re-challenge with sildenafil. Adverse events were significantly greater in the treatment group. These adverse events consisted mostly of nausea, flushing, and diaphoresis.

Invasive therapies

Further therapies utilizing a vacuum constriction device, intraurethral alprostadil, intracavernosal injection, or penile prosthesis placement are beyond the scope of this review. It should be noted that each of these can be used as monotherapy or in combination with PDE5-i. Patients may wish to proceed to one of these options rather than have multiple attempts with a PDE5-i, leading to the important role of personalized medicine in managing men failing PDE5-i treatment. No direct comparisons of these therapies with options to improve response to PDE5-i currently exist.

Medical society guidelines

A review of the AUA guidelines on management of erectile dysfunction supports the role of PDE5-i therapy as the first step in medical management for men without contraindications [Montague *et al*. 2005]. The guideline emphasizes the role of patient and partner education on the risks and benefits of PDE5-i and the application of a step-wise approach utilizing concurrent lifestyle management with medical therapy. The panel was in general agreement that an attempt should be made to ensure the trial of the PDE5-i was adequate and that subsequently therapy should be guided by patient choice. Testosterone is not recommended for use in eugonadal men, however no recommendation is provided for hypogonadal men.

The International Society for Sexual Medicine (ISSM) issued a clinical guideline in 2004 which does not specifically address PDE5-i as the initial treatment of choice, although a multi-step approach is employed [Lue *et al*. 2004]. After addressing comorbidities and manageable risk factors, therapy "should be viewed as restoration of a satisfactory sexual life, not only a rigid erection". For patients not satisfied with results, re-education on optimal use of the trialed treatment, and treatment for concurrent hypogonadism is recommended.

The Endocrine Society clinical practice guideline on testosterone therapy [Bhasin *et al*. 2006] recommends that a clinician offer testosterone therapy to patients with erectile dysfunction and unequivocal low testosterone levels. It is also recommended that patients with low libido be offered testosterone replacement.

Utilizing the reviewed publications and the clinical guidelines from the AUA, ISSM, and Endocrine Society, a noninvasive treatment strategy is proposed (Figure 1). This strategy stresses patient education and lifestyle adjunctive measures in preference to rapid invasive treatment.

Conclusion

Between 30 and 40% of patients fail initial attempts to manage erectile dysfunction with PDE5-i. Many of these patients can be salvaged with further noninvasive management. Specific patient instruction regarding timing of medication

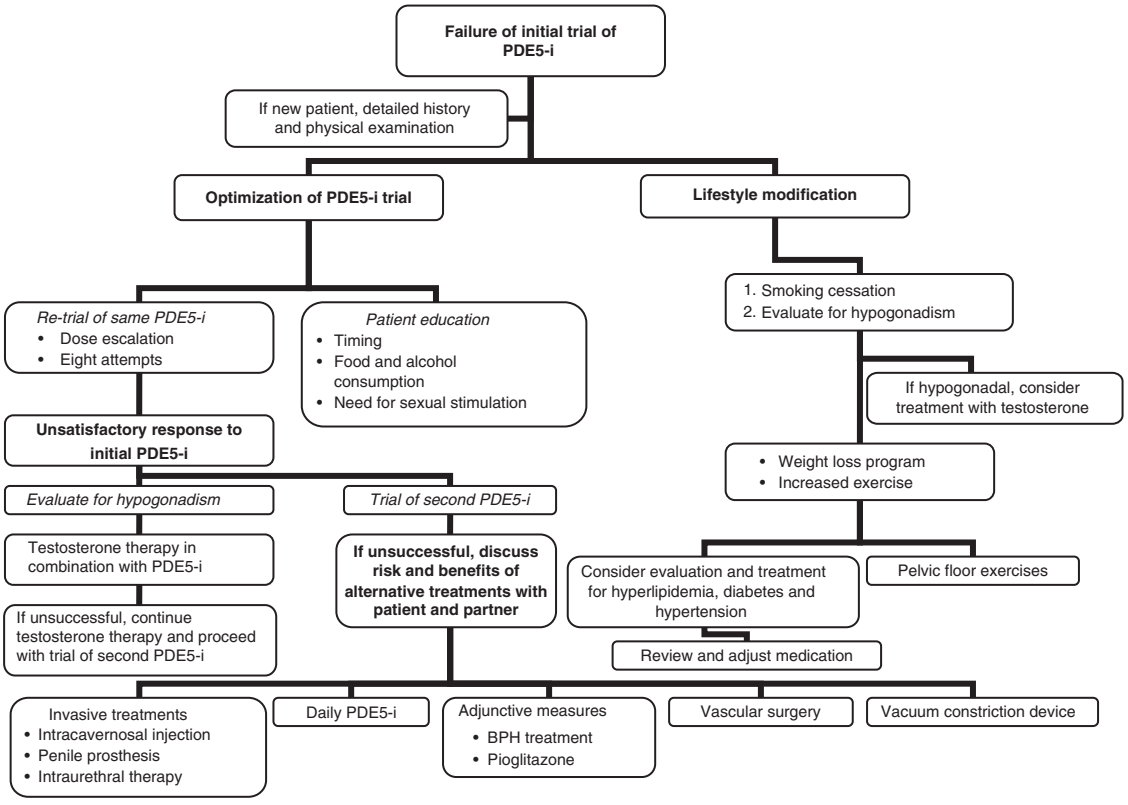

Figure 1. Proposed noninvasive treatment strategy.

dosing and effect of food and alcohol are often inadequate at the time of initial prescribing. Patients should expect that it may take up to eight attempts prior to achieving the benefit of a PDE5-i. Lifestyle changes improve erectile response and overall health. Pelvic floor exercises have been shown to increase erectile responsiveness. Daily dosing of a PDE5-i may provide benefit for up to 41% of men. Switching the PDE5-i has been shown to provide response rates between 12% and 61% in patients failing a previous PDE5-i. Finally, treatment of hypogonadism and treatment with pioglitazone, doxazosin, or bremelanotide have been shown to improve PDE5-i responsiveness in small clinical studies but remain to be substantiated. High dose PDE5-i treatment carries increased rates of adverse effects, and patient drop-out increases. Finally, the authors recommend a 'personalized medicine' approach be taken when counseling patients initially failing PDE5-i, as not all patients will be tolerant of the trials necessary to achieve success with a noninvasive approach. Further trials are necessary to determine which patient characteristics lend to a poor response regardless of the PDE5-i used, in order to direct these patients to a more effective therapy.

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