

## Treatment Strategy for Non-Responders to PDE5 Inhibitors

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Currently, phosphodiesterase type 5 (PDE5) inhibitors are the initial treatment option for erectile dysfunction. The reported efficacy of PDE5 inhibitors is about 70%, although it is significantly lower in difficult-to-treat subpopulations. Treatment failures might be due to the severity of the underlying pathophysiology, improper use of medication, unrealistic patient expectations, difficult relationship dynamics, severe performance anxiety, and other psychological problems. Physicians must address these issues to identify true treatment failures attributable to the drugs. This article discusses factors that might affect the response to PDE5 inhibitors and develops a strategy to maximize the overall efficacy of PDE5 inhibitors in initial non-responders to PDE5 inhibitors.

**Key Words:** Erectile dysfunction; Phosphodiesterase type 5 inhibitors; Sildenafil; Tadalafil; Vardenafil

### INTRODUCTION

There is robust evidence that phosphodiesterase type 5 (PDE5) inhibitors are effective, safe, and well-tolerated in the treatment of erectile dysfunction (ED). PDE5 inhibitors are the first-line therapy for most men with ED who do not have a specific contraindication to their use.<sup>1</sup> Although many treatment algorithms provide a step-wise approach to the management of ED that can be useful clinically, a panel of experts at the International Consultation on Erectile Dysfunction recommended oral agents as a first-line treatment for ED independent of etiology.<sup>2</sup> In addition, most patients prefer to take PDE5 inhibitors, since they are easy to use and very effective. However,

the efficacy of PDE5 inhibitors is significantly lower in difficult-to-treat subpopulations.<sup>3</sup> Although some alternatives exist for patients who are proven non-responders to PDE5 inhibitors, such as vacuum constriction devices, intracavernous injections of vasoactive agents (such as prostaglandin E1), transurethral delivery of alprostadil, implantation of penile prostheses, and venous or arterial surgery, failure to achieve successful intercourse after using the maximum recommended dose of PDE5 inhibitors is always a problem if the patient does not desire such alternative treatments. This article examines the factors that might affect the response to PDE5 inhibitors and develops a strategy to maximize the overall efficacy of PDE5 inhibitors in initial non-responders to PDE5 inhibitors.

Received: Feb 25, 2013; Accepted: Mar 4, 2013

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## REASONS FOR AN INITIAL NON-RESPONSE TO PDE5 INHIBITORS

### 1. Comorbidities

Several recent studies have suggested that ED can be the initial clinical presentation of underlying cardiovascular disease (CVD).<sup>4</sup> Endothelial dysfunction is a major common mechanism in the development of ED and CVD. Metabolic syndrome (MS) is defined as the clustering of several cardiovascular risk factors, including visceral obesity, hypertension, dyslipidemia, and glucose intolerance. These components are also risk factors for ED. Esposito et al<sup>5</sup> reported that the proportion with ED was higher in men with MS. Therefore, it is possible that patients with MS respond differently to PDE5 inhibitors. Suetomi et al<sup>6</sup> demonstrated the negative impact of MS on the response to sildenafil.

### 2. Inappropriate use

Patients with ED might receive inadequate instructions regarding the use of their prescriptions. In one study of 100 consecutive sildenafil non-responders, 56 patients used sildenafil inappropriately: 45 had never used the highest recommended dose (100 mg); 32 had taken the pill with a full stomach right after a meal; 22 had taken the pill just before initiating sexual activity; and 12 were not aware that sexual stimulation was mandatory to achieve an erection.<sup>3</sup> In another study, Hatzimouratidis et al<sup>7</sup> identified the inappropriate use of tadalafil and vardenafil in 32% and 38% of patients, respectively. Two reasons for inappropriate use were identified: most patients had tried fewer than four attempts and the highest recommended dose had not been used by 31.3% and 7.9% of the patients in the tadalafil and vardenafil groups, respectively. This finding might be due to the fact that the vast increase in men seeking help for ED has resulted in widespread prescription of PDE5 inhibitors by physicians who do not have the background knowledge or time to educate and treat ED patients appropriately.<sup>8</sup>

### 3. Misdiagnosis

Some patients are initially misdiagnosed as non-responders to PDE5 inhibitors. These include patients with hypogonadism or hyperprolactinemia who need specific

hormonal treatment to improve erectile function (EF). In animals, the pharmacological activity of PDE5 inhibitors appears to be androgen-dependent;<sup>1,9</sup> indeed the expression of PDE5 in humans also appears to be androgen-dependent.<sup>1</sup> Testosterone deficiency seems to predict a poor response to sildenafil<sup>10-12</sup> or tadalafil<sup>13</sup> and the addition of testosterone seemed helpful in five uncontrolled studies.<sup>12-14</sup> In addition, some patients with Peyronie's disease need treatment for penile curvature or pain during intercourse and other patients do not have ED, but they experience ejaculatory dysfunction or sensory disturbances.

### 4. Psychological and partner issues

Patients can have unrealistic expectations, such as considering the drug an aphrodisiac, fear of possible complications or side effects of the drugs, and anxiety about their new sexual life after long-term abstinence due to ED, or have unaddressed psychological issues. Partner issues are equally important and should be addressed. These include female sexual function issues, such as pain, anorgasmia, vaginal dryness, or lack of sexual interest.

## MANAGEMENT OF NON-RESPONDERS TO PDE5 INHIBITORS

### 1. Patient education

ED is a chronic disease; follow-up visits are mandatory, not only to improve physician-patient communication, but also to provide continuing education to patients. Critical aspects in the management of ED patients, such those included in the acronym 'FAST' (Follow-up, Adjusting time of administration, Sexual stimulation, and Titration to the maximum tolerated dose) are still essential.<sup>15</sup> In one study, following appropriate dose titration to the maximum tolerated dose and providing instructions on administration (use at least four doses), 32 ~ 44% of patients who were non-responders to tadalafil or vardenafil initially, responded to PDE5 inhibitors.<sup>7</sup>

Most labeling on PDE5 inhibitors indicates that the drugs can be taken with or without food, although there is a precaution that a high-fat calorie meal might delay the onset of action. Such high-fat diets might be common, and the response to PDE5 inhibitors might be suboptimal if patients

are unaware of this. In addition, insufficient sexual stimulation after PDE5 inhibitor administration is an important cause of a non-response to PDE5 inhibitors, especially in elderly patients. Physicians must be aware of these facts and properly inform patients about adequate administration of PDE5 inhibitors, despite labeling information.

## 2. Improvement of related comorbid conditions

Several studies have revealed that the correction of hyperlipidemia improves the response to PDE5 inhibitors in hypercholesterolemic men with ED who were not initially responsive to PDE5 inhibitors. In a study of adjunctive atorvastatin for restoring normal EF in hypercholesterolemic (low-density lipoprotein cholesterol >120 mg per 100 ml) sildenafil non-responders, the atorvastatin group had significantly greater improvements in all International Index of Erectile Function (IIEF)-5 questions and the global efficacy question.<sup>16</sup> In a study of the effect of correcting serum cholesterol levels on EF and sildenafil treatment in patients with ED who had only hypercholesterolemia as a risk factor for ED, correcting the serum cholesterol level with atorvastatin improved EF. Furthermore, atorvastatin improved the effects of sildenafil on EF in hypercholesterolemic patients with ED.<sup>17</sup> In line with this, Suetomi et al<sup>6</sup> demonstrated the negative effect of MS on the response to sildenafil. Although the detailed mechanism is unclear, this result might motivate men to reduce these risk factors, especially those who did not respond to treatment with a PDE5 inhibitor initially.

## 3. Normalizing testosterone levels

Hypogonadal men who are non-responders to PDE5 inhibitors might benefit from normalization of testosterone levels. Some patients who failed to respond to treatment of ED with PDE5 inhibitors might have an associated testosterone deficiency. The TADTEST study revealed that addition of testosterone to treatment with PDE5 inhibitors is beneficial in men with low baseline testosterone levels (<3 ng/ml).<sup>2</sup> The lower the baseline testosterone level, the better is the effect. This agrees with published definitions of testosterone deficiency of a threshold of 3 ng/ml.<sup>18</sup> The results of the TADTEST study correspond with the results of Aversa et al,<sup>19</sup> who observed that short-term testosterone administration in patients with ar-

teriogenic ED and low-normal androgen levels increases testosterone and free testosterone levels and improves the erectile response to sildenafil, likely by increasing arterial inflow to the penis during sexual stimulation. In accordance with this study, Shabsigh et al<sup>20</sup> demonstrated that hypogonadal men (morning serum total testosterone  $\leq$  4 ng/ml) with a confirmed lack of response to sildenafil monotherapy, a daily dose of 1% testosterone gel as adjunctive therapy to 100 mg sildenafil during a 12-week period showed greater improvement in EF compared to those who received a placebo. Given all this, it seems prudent to screen men presenting with ED for hypogonadism before initiating therapy.

## 4. Switching PDE5 inhibitors

Compared with sildenafil and vardenafil, tadalafil is characterized by a long elimination half-life that allows for more flexibility of timing for patients. The duration of action of tadalafil is much longer than that of other PDE5 inhibitors; consequently, it has become one of the choices of patients who are proven non-responders to relatively short-acting PDE5 inhibitors.<sup>21</sup> Sildenafil and vardenafil have similar molecular structures, but tadalafil differs in structure, which is reflected in its pharmacokinetic profile. Regarding its onset of action, *i.e.*, achieving an erection that leads to successful intercourse, sildenafil and vardenafil both have half-lives of approximately 4 h, while the half-life of tadalafil is approximately 18 h. Another difference is that fatty food affects the pharmacokinetic profiles of sildenafil and vardenafil, but not that of tadalafil.<sup>22</sup>

## 5. Daily or continuous use of PDE5 inhibitors

Daily dosing of PDE5 inhibitors has recently come to our attention. Continuous inhibition of PDE5 results in a permanently high concentration of cyclic guanosine monophosphate, offering ED patients a higher level of efficacy and flexibility in sexual involvement. McMahon<sup>23</sup> previously treated non-responders to on-demand tadalafil with continuous use on a daily basis at flexible doses of 10 or 20 mg of tadalafil for 12 weeks. Daily tadalafil significantly improved ( $p < 0.001$ ) the IIEF EF domain score and Sexual Encounter Profile question 3, compared with on-demand tadalafil. In the study by Hatzimouratidis et al,<sup>7</sup> non-responders to tadalafil or vardenafil on-demand

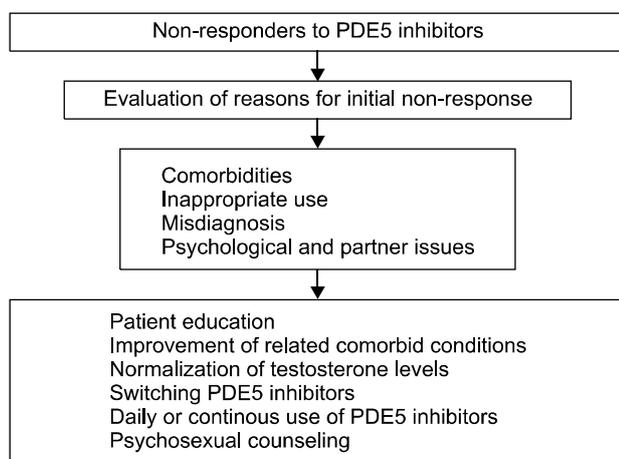
therapy were re-challenged with continuous the use of 20 mg of tadalafil every other day or vardenafil 20 mg every day for 2 consecutive weeks. Following continuous administration, 11.1% of patients in the tadalafil group and 18.2% in the vardenafil group converted to responders. Although the data on the systemic effects of the continuous inhibition of PDE5 are limited, chronic administration of PDE5 inhibitors has been shown to improve endothelial function in patients at increased cardiovascular risk.<sup>24</sup> Further research into the continuous administration of PDE5 inhibitors is needed, as well as on the possible benefits of daily use in patients who initially have not responded to PDE5 inhibitors.

## 6. Psychosexual counseling

When a doctor simply prescribes a PDE5 inhibitor, he deals with only one aspect of a complex problem. Proper patient counseling and follow-up is necessary to overcome psychological and partner issues. Psychosexual counseling is an important tool in the overall therapy and eventual success of treatment for both the patient and his partner. Counseling combined with a PDE5 inhibitor seems to offer an advantage over either method alone.

## CONCLUSIONS

Although some alternatives exist for patients who are proven non-responders to PDE5 inhibitors, such as vacuum constriction devices, intracavernous injections of



**Fig. 1.** Treatment strategy for non-responders to PDE5 inhibitors. PDE: phosphodiesterase.

vasoactive agents (such as prostaglandin E1), transurethral delivery of alprostadil, implantation of penile prostheses, and venous or arterial surgery, failure to achieve successful intercourse after using the maximum recommended dose of PDE5 inhibitors is always a problem if the patient does not desire such alternative treatments. The treatment strategy we propose here might maximize the response rate to PDE5 inhibitors (Fig. 1). The reasons for the inappropriate use of oral drugs should be considered. Testosterone levels should be assessed and supplemented in hypogonadal men. Second- and third-line treatment alternatives should be offered to true non-responders.

## ACKNOWLEDGEMENTS

This study was supported by the clinical research grant from Pusan National University Hospital (2012).

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