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Review Article

Erectile dysfunction patients who are phosphodiesterase enzyme type 5 inhibitors (PDE5Is) non responders

Hytham Abdelrahman, Amr Abdelhamed Ali, Reham Ezz Eldawla, Essam Nada.

Department of Dermatology, Venereology, and Andrology, Sohag Faculty of Medicine. Sohag University.

Abstract:

Erectile dysfunction (ED) has many definitions, one of these accepted definition that the male is unable to initiate and/or preserve an erection for ideal sexual intercourse satisfying for both partners. There are many lines for ED treatment, oral phosphodiesterase type 5 inhibitors (PDE5Is) represent the corner stone for ED treatment. Intra cavernous injections, vacuum constriction device & surgical implantation of penile prosthesis are another methods for ED treatment. Authors failed to define exactly the failure of PDE5-I therapy in ED. However, many reviews reported two types of PDE5Is non responders. As regard the cause making ED patients non responders to PDE5Is, multiple etiological factors have a role. Four strategies were reported about in literatures as trial to solve PDE5i non responders problem including lifestyle adjustments, psychological assessment, comorbidities treatment & non drug therapeutic interventions. Patient counseling to know and resolve patients' concerns and ensure the hopped success of treatment. Good communication and regular follow up should be established.

Keywords: Erectile dysfunction, PDE5Is non responders, Sexual problems

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Introduction:

Erectile dysfunction (ED) is defined as the persistent inability to attain and/or preserve sufficient erection to permit satisfactory sexual performance for both partners.⁽¹⁾ ED is a worldwide problem affecting men everywhere causing social and psychological distress affecting the quality of life.⁽²⁾ Aging, metabolic syndrome, diabetes mellitus, obesity, lack of exercise, and smoking considered the main risk factors for ED.⁽³⁾

First-line treatment of ED is usually with oral phosphodiesterase type 5 inhibitors. When PDE5Is fail to solve the problem, intra cavernous injections with different

vasodilating substances and surgical implantation of penile prosthesis may have a role. Sometimes these invasive methods refused by some patients so, there are many new treatment modalities that have become popular in recent years like low-intensity extracorporeal shock wave therapy, platelet rich plasma (PRP), stem cells and hyp-erbaric oxygen therapy (HBOT).⁽⁴⁾

Definition of PDE5Is responders and non responders

The United States food and drug administration (US FDA) guidance (2009) on

patient reported outcome development has emphasized that it is important to define a treatment responder in a transparent, evidence-based manner, and validating the approach using anchor-based methods.⁽⁵⁾

As we know, authors are unable to define the failure of PDE5Is therapy for ED. However, **Carson et al. (2004)** proposed definition for the patients who are non responder to oral pharmacotherapy: ‘an insufficient erection after at least separated four attempts using the maximum tolerated drug dose in addition to following manufacturer’s guidelines respecting the timing relative to fully or empty stomach, alcohol ingestion, use of concomitant drugs and finally adequate sexual stimulation & arousal.’⁽⁶⁾

To have an accepted objective criteria for researchers or clinicians to make a decision whether efficient ED treatment response has been achieved or no, **Yang et al. (2013)** developed and validated a novel method of defining responders to ED treatment depending on many approved questioners as multiple International Index of Erectile Function (IIEF) criteria and Sexual Encounter Profile (SEP) question and Global Assessment Question (GAQ) for validation.⁽⁷⁾

Finally **Yang** reached to that treatment responders to ED treatment can be defined as a complete responders (erectile function (EF) ≥ 26), partial responders (EF < 26; met minimal clinically important difference criteria), or non-responder following treatment (EF < 26; did not meet minimal clinically important difference).⁽⁷⁾

Classification of PDE5Is non responders:

PDE5Is non responders can be classified in two main types:⁽⁸⁾

- 1- Real non responders: mostly patients who suffer from severe end-organ failure or pharmacogenetic anomalies.
- 2- pseudo-non responders: patients who are affected by reversible risk factors such as inappropriate counseling, sedentary lifestyle, presence of uncontrolled associated comorbidities and/or intake of concomitant high risk drugs, misdiagnosis, psycho social issues, personal related factors and partner related factors.

Etiology of PDE5Is non responders:

As reported in literatures, patients who are non-responders to PDE5Is have multiple etiological factors as shown in the table below.⁽⁸⁾

Table 1: Etiological factors of PDE5Is non responders.⁽⁸⁾

<p>1) Inadequate instructions:</p> <ul style="list-style-type: none"> *Timing relative to meals *Inadequate sexual stimulation or arousal *Heavy alcohol *Insufficient trial attempts *Physician's lack of training/education *Physician's lack of time to discuss with/educate patients *Insufficient clarification about safety *Failure to understand and remember instructions *Failure of the patient to adhere to drug use instructions 	<p>2) Misdiagnosis:</p> <ul style="list-style-type: none"> *Desire disorder *Premature ejaculation *Sexual orientation problems *Peyronie's disease
<p>3) Uncontrolled associated comorbidities:</p> <ul style="list-style-type: none"> *Diabetes *Hypogonadism *Hyperprolactinemia *Hypertension *Coronary artery disease *Smoking *Obesity *Metabolic syndrome *Lipid abnormalities *Benign prostatic hyperplasia *Drug intake 	<p>4) Severe ED (severe end-organ failure):</p> <ul style="list-style-type: none"> *Severe peripheral vascular disease *Severe diabetes mellitus with neuropathy *Severe endothelial dysfunction *Metabolic syndrome *Severe autonomic neuropathy *Radical prostatectomy with bilateral injury of neurovascular bundle *Radiotherapy for prostate cancer
<p>5) Psychosocial issues:</p> <ul style="list-style-type: none"> *Fear of possible complications or side effects *Anxiety about new sexual life *Unaddressed psychological issues such as guilt or religious concerns about engaging in sexual intimacy, minor depression, or post-traumatic stress disorder *Unrealistic expectations 	<p>6) Partner-related factors:</p> <ul style="list-style-type: none"> *Refusal of intercourse and relationship problems *Disability/associated risk factors *Female sexual dysfunctions *Lack of involvement in the treatment
<p>7) Pharmacogenetic and pharmacogenomic factors:</p> <ul style="list-style-type: none"> *Angiotensin-converting enzyme I/D polymorphisms *G-protein subunit Gb3 polymorphisms *Endothelial nitric oxide synthase polymorphisms *Vascular endothelial growth factor polymorphisms 	

ED, erectile dysfunction; I/D, insertion/deletion.

Management:

True non responders to PDE5Is mostly have a severe end-organ failure or pharmacogenetic anomalies, whereas pseu-

do non responders to PDE5Is are mostly affected by correctable and reversible risk factors such as inappropriate coun-

seling, sedentary lifestyle, presence of uncontrolled associated comorbidities and/or intake of concomitant high risk drugs, misdiagnosis, psycho social issues, personal related factors and partner related factors. Awareness of exactly the nature of the etiological factors of failure to PDE5Is either correctable or non-correctable will help to improve the treatment outcome.⁽⁸⁾

As regard management of PDE5I non responders, **Xiaoqing et al (2020)** published four strategies to treat PDE5I non responders.⁽⁹⁾

- 1- First line strategy include lifestyle adjustments and strict following of pharmacotherapy with PDE5Is including sufficient medication trials, increased PDE5Is doses, different dosing regimens, different PDE5Is and the combined use of long-acting and short-acting PDE5Is.
- 2- Second line strategy when the ED patient has clear mental disorder, we should not ignore but should focus on the patient's psychology and give corresponding suitable treatment such as attaching importance to the partner's role and providing psychological intervention as drugs, sexual counseling and cognitive behavioral therapy. Also other strategies to improve pharmacotherapy with PDE5Is and lifestyle adjustments should be added.
- 3- Third line strategy when ED patients complain of comorbidities, (comorbidity-related strategies) such as the selection of PDE5Is with greater effects on ED and the management of comorbidities of ED including associated medication modifications and combining PDE5is with other non-PDE5i drugs. Also improving pharmacotherapy with PDE5Is and lifestyle adjustments should be fully considered as adjuvant strategies.

- 4- Fourth line strategy in neglected advanced conditions, non-drug therapeutic approaches as vacuum constriction devices with or without PDE5Is can be selected according to the actual treatment profile of each PDE5I non responder.

It is worth to know that when we treat every PDE5I non responder, patient management should be of great concern. Follow-up visits regularly should be carried out to discover any shortage in the ED treatment process. Patient counseling to know and resolve patients' concerns and ensure the hopped success of treatment. Good communication and regular follow up should be established.

Conclusion:

Erectile dysfunction (ED) is a common sexual problem affecting male worldwide characterized by inability to attain and/or maintain erection sufficient for satisfactory sexual intercourse causing psychological and social troubles. Many factors cause ED as DM, HTN, smoking, dyslipidemia, psychological problems, drugs and many other factors. Many lines for treatment of ED are present but still the corner stone is PDE5Is.

Non responders to PDE5Is are present and defined as inadequate erectile response after at least four attempts using the highest tolerated drug dose in association with manufacturer's guidelines with respect to timing relative to meals, alcohol ingestion, use of concomitant medications and adequate sexual stimulation & arousal.

Two types of PDE5Is non responders are present, real non responders as end organ failure & pseudo-non responders as correctable factors. As regard the management of PDE5i non responders, four strategies to treat PDE5I non responders including lifestyle adjustments, psychological assessment, comorbidities treat-

ment & non drug therapeutic interventions.

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