PDE5 INHIBITORS NON-RESPONDERS

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INTRODUCTION

• Erectile dysfunction (ED), is a sexual disorder consisting of penile rigidity insufficient for satisfactory sexual intercourse.
• Currently affects 52% of 40-70-year-old men.
• Aging and abundance of comorbidities increase in the prevalence of ED.
• ED is a symptom, not a disease.
• Phosphodiesterase type 5 inhibitor (PDE5-i) is the first line therapy for the treatment of erectile dysfunction.

• Most initial prescriptions for PDE5-i are by primary care practitioners.

• Urologists should manage patient who has failed initial therapy with PDE5-i. (Gregory and Bahnson 2010)

• Up to 35% of these patients fail to respond and medication re-prescription rates drop to 30%.
SILDENAFIL

- Launched in 1998, was the first PDE5 inhibitor available on the market.
- Effective from 30-60 min after administration.
- Reduced efficacy after a heavy, fatty meal due to prolonged absorption.
- Administered in 25, 50 and 100 mg doses.
- Recommended starting dose is 50 mg and adapted according to the patient’s response and side-effects.
- Efficacy may be maintained for up to 12 h.
"Ok, This Viagra works now we need to calculate the dosage"
TADALAFIL

- Licensed for treatment of ED as of February 2003, and is effective from 30 min after administration, with peak efficacy after about 2 hours.
- Efficacy is maintained for up to 36 hrs and is not affected by food.
- Administered in 10 and 20 mg doses.
- The recommended starting dose is 10 mg and adapted according to the patient’s response and side-effects.
VARDENAFIL

• Commercially available in March 2003,
• Effective from 30 min after administration.
• Reduced effect by a heavy, fatty meal (> 57% fat).
• Administered in 5, 10 and 20 mg doses.
• The recommended starting dose is 10 mg and adapted according to the patient’s response and side-effects.
• It is 10-fold more potent than sildenafil.
## Pharmacokinetics of the three PDE5 inhibitors

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Tmax</th>
<th>Earliest onset of action (min)</th>
<th>T1/2 (h)</th>
<th>Duration of effect (h)</th>
<th>Recommended dosing time (h) prior to intercourse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil 100 mg</td>
<td>1</td>
<td>30</td>
<td>4</td>
<td>4–6 (up to 12)</td>
<td>1</td>
</tr>
<tr>
<td>Tadalafil 20 mg</td>
<td>2</td>
<td>20</td>
<td>17.5</td>
<td>24–36 (up to 72)</td>
<td>0.5–12</td>
</tr>
<tr>
<td>Vardenafil 20 mg</td>
<td>0.7</td>
<td>10</td>
<td>4.5</td>
<td>5–7 (up to 12)</td>
<td>0.5–1</td>
</tr>
</tbody>
</table>
Factors affecting the choice of PDE5 inhibitors.

**Medication issues:**
- Efficacy
- Safety
- Tolerability
- Duration of action
- Food interactions
- Reputation
- ‘Newness’
- Cost.
Patient issues:
- Marital status
- Culture
- Finances
- Comorbidity
- Expectations

Physician issues:
- Experience
- Familiarity
- Expertise
Reasons for early discontinuation of PDE5 inhibitors therapy

- Efficacy below expectations.
- High cost.
- Loss of interest in sex.
- Inconvenience in obtaining the drugs.
- Recovery of erectile ability.
- Partner reluctance.
- Side effects.
- Other reasons
HOW TO ASSESS TREATMENT RESPONSE TO PDE5 INHIBITORS?
• **International Index of Erectile Function (IIEF)\)**

  • Precede all questions listed below with the phrase, “Over the past 4 weeks, . . .”
  • Q1. How often were you able to get an erection during sexual activity?
  • Q2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
    - 0 = No sexual activity; 1 = Almost never/never; 2 = A few times (much less than half the time); 3 = Sometimes (about half the time); 4 = Most times (much more than half the time); 5 = Almost always/always
  • Q3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
  • Q4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
    - 0 = Did not attempt intercourse; 1 = Almost never/never; 2 = A few times (much less than half the time); 3 = Sometimes (about half the time); 4 = Most times (much more than half the time); 5 = Almost always/always
  • Q5. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
    - 0 = Did not attempt intercourse; 1 = Extremely difficult; 2 = Very difficult; 3 = Difficult; 4 = Slightly difficult; 5 = Not difficult
  • Q15. How do you rate your confidence that you could get and keep an erection?
    - 1 = Very low; 2 = Low; 3 = Moderate; 4 = High; 5 = Very high
• International Index of Erectile Function (IIEF) is considered the gold standard tool for assessing ED.

• Currently, **minimal clinically important difference** (MCID) used to define treatment responder.

• MCID is defined as change in the IIEF-EF domain score of 4 points or more.
1-Primary Efficacy Objective:
• change in the IIEF- EF

2- Secondary Efficacy Objective:
improvement in sexual activity according to
• SEP- Sexual Encounter Profile: Questions 2 and 3
• – GAQ- Global Assessment Questions: 1 and 2
• – EHS- Erection Hardness Score
• **Sexual Encounter Profile (SEP2—SEP3)**

- **SEP-Q2**: Over the past 4 weeks, were you able to insert your penis into your partner's vagina?
  
  Yes......... No.........

- **SEP-Q3**: Over the past 4 weeks, did your erection last long enough for you to have successful intercourse?
  
  Yes......... No.........
• **Global Assessment Question (GAQ)**

• **GAQ-Q1**: Over the past 4 weeks, has the treatment you have been taking improved your erectile function?
  Yes......... No.........

• **GAQ-Q2**: If yes, has the treatment improved your ability to engage in sexual activity over the past 4 weeks?
  Yes......... No.........
EHS- Erection Hardness Score

• How would you rate the hardness of your erection?
  0: Penis does not enlarge
  1: Penis is larger but not hard
  2: Penis is hard but not hard enough for penetration
  3: Penis is hard enough for penetration but not completely hard
  4: Penis is completely hard and fully rigid
CLASSIFICATION OF RESPONDERS

- Responders are classified into:
- COMPLETE RESPONDERS.
- PARTIAL RESPONDERS.
- NON-RESPONDERS:
  1. True non-responders.
COMPLETE RESPONDERS

- Erectile function is > 26.
- Characterized by:
  - Younger patients.
  - Had mild ED at base line
  - ED of short duration.
  - Slightly lower numbers of comorbidities and concomitant medication use.
NON-RESPONDERS

• Which is either true or pseudo-non-responders
• Between 30% and 40% of a ED patients do not sufficiently respond to the maximum dose of the PDE5 inhibitors.
• Responsiveness to PDE5 inhibitors depends on the underlying etiology of ED.
• Erectile function is < 26 not meeting MCID criteria and characterized by:
  - older patients.
  - ED of long duration.
  - More comorbidities.
  - Concomitant medication use.
PARTIAL RESPONDERS:

Erectile function < 26 but meeting MCID criteria.

- Fell in between complete responders and non-responders.
- Less comorbidities and concomitant medication use.
TRUE NONRESPONDERS

• True non-responders mostly have severe end-organ failure.

• PDE5 inhibitor non-responders show severe veno-occlusive dysfunction and/or severe impairment of penile arterial supply, “arteriogenic” ED
TRUE NON-RESPONDERS

• “Any patient who, after 4-8 successive or closely timed trials of the maximum tolerated dose of the medication with respect to timing relative to meals, alcohol ingestion, use of concomitant medications and adequate sexual stimulation, is unable to achieve or sustain adequate penile rigidity until completion of sexual performance.” is considered true non-responder.
“PSEUDO-NON-RESPONDERS”

- Non-responders may be converted into responders through appropriate counseling regarding specific drug-related pharmacokinetics/dynamics, change of sedentary lifestyle, adequate treatment of concomitant diseases, and/or exchange of concomitant medications in favor of more erection protective drugs.
• **CAUSES OF FAILURE OF PDE5 INHIBITORS:**
  (CHELSEA et al 2006)

1 - Severe ED at presentation.
2 - Comorbidities
3 - Anxiety of performance.
4 - Unidentified hypogonadism.
5 - Inadequate patient education.
6 - Incorrect usage of the drugs.
7 - Development of tachyphylaxis. (rapidly diminishing response to successive doses of a drug, rendering it less effective)
8 - Psychosocial factors.
## Modifiable Risk Factors for and Their Management

<table>
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<tr>
<th>RISK FACTOR</th>
<th>STRATEGY</th>
</tr>
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<tbody>
<tr>
<td>SEDENTARY LIFE</td>
<td>Increase physical activity</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Quit smoking/use of patch</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Improved control</td>
</tr>
<tr>
<td>Depression</td>
<td>Treatment of depression</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Testosterone replacement</td>
</tr>
<tr>
<td>dyslipidaemia</td>
<td>Control</td>
</tr>
<tr>
<td>Alcoho</td>
<td>Abstinence from alcohol</td>
</tr>
<tr>
<td>Overweight or obesity (BMI &gt; 26.9 kg/m²)</td>
<td>Weight loss</td>
</tr>
</tbody>
</table>
Reasons for initial Non-response to PDE5 inhibitors

• **CO-MORBIDITIES:**
  • Endothelial dysfunction is a major mechanism in the development of ED
  • Metabolic syndrome :
    1- Obesity
    2- Hypertension.
    3- Dyslipidaemia.
    4- Diabetes mellitus.
• **MISDIAGNOSIS:**
  • Patients are initially misdiagnosed as non-responders to PDE5 inhibitors.
  • Hypogonadism or hyperprolactinaemia need specific hormonal treatment to improve erectile function.
  • Pharmacological activities of PDE5 inhibitors is androgen dependent.
  • Testosterone deficiency predicts poor response to PDE5 inhibitors.
• **PSYCHOLOGICAL AND PARTNER ISSUES:**

Patients can have unrealistic expectations such as:

1- Considering drug an aphrodisiac.

2- Fear of complications or side effects.

3- Anxiety about new sexual life (after long abstinence period).

• Partner issues (female sexual dysfunction) as pain, anorgasmia, vaginal dryness, or lack of sexual interest.
INAPPROPRIATE DRUG USE

• Patients fail to respond to a PDE5 inhibitor due to inefficacy of the drug or incorrect drug use.

1- Inefficiency of the drug: there is a very large ‘black market’ in PDE5 inhibitors, as the amount of active drug in these medications varies enormously.

• Check how and from which source the patient has obtained his medication and be sure of licensed medication

2- Incorrect drug use (inadequate patient counseling):
1- Incorrect drug use

• failure to use adequate sexual stimulation.

• PDE5 inhibitors depend for their action upon the release of nitric oxide(NO) by the parasympathetic nerves of the penis.

• Nitric oxide release is enhanced by sexual stimulation, and without adequate sexual stimulation (and NO release), the drugs cannot work.
2- Time Failure:

• failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

• Oral PDE5 inhibitors take different times to reach maximal plasma concentrations.

• Most patients require a longer delay between taking the medication, 60 -120 min for sildenafil and vardenafil and up to 2 h for tadalafil.
3- Inadequate dose

- For financial reasons, or fear of side effects, some physicians may prescribe only the lower doses of a medication.
- Check that the patient has had an adequate trial of the maximal dose of the drug.
- Adequate trial involves at least 4-8 attempts with a particular drug.
MANAGEMENT OF NON-RESPONDERS TO PDE5 INHIBITORS

• 1- Patient education.
• 2- Improved of related co-morbid conditions.
• 3- Normalizing testosterone level.
• 4- Switching PDE5 inhibitors.
• 5- Daily or continuous use of PDE5 inhibitors.
• Psychosocial counseling.
• Combined therapy.
PATIENT EDUCATION

- Patient education and life style modification are essential for improvement of response to PDE5 inhibitors.
- Improvement of physician- patient communication.
- Provide continuous education to the patient.
- Adjusting time of administration.
- Advice sexual stimulation.
- Titration to maximum tolerated dose.
- Avoid fatty diet as it delay the onset of action.
• Use maximum dose for 4-8 attempts
• Use licensed medication.
• Patients taking tadalafil were advised to wait at least 2 h between oral ingestion and attempting intercourse.
• Patients taking vardenafil were advised to use the drug only after a fast.
• Smoking cessation, weight loss.
• increased physical activity.
• pelvic floor muscle exercises have shown benefit in returning erectile function.
• Significant improvement was seen at the 6 months assessment.
IMPROVEMENT OF RELATED CO-MORBIDITIES

1- Treatment of obesity by weight loss.
2- Control of hypertension.
3- Control of dyslipidaemia.
4- Control of diabetes mellitus.
NORMALIZING TESTOSTERONE LEVEL

• Low serum testosterone associated with impaired cavernous vasodilatation.
• Hypogonadal men non-responders to PDE5 inhibitors benefit from normalization of testosterone level with 1% hydrochloric testosterone gel in treatment of ED.
• Testosterone improve the action of PDE5 inhibitors.
SWITCHING PDE5 INHIBITORS

• Sildenafil should be considered first line therapy.
• Patients should be exposed to 4 - 8 maximum doses of sildenafil before switching to an alternative PDE5 inhibitor.
• Patients should be followed up within 6 weeks of commencing therapy to assess response.
• Non responders to sildenafil can be switched to tadalafil and assessed according to response.
SWITCHING PDE5 INHIBITORS

- Tadalafil has long elimination half time allowing for more flexibility of timing for patients
- Duration of action of tadalafil is longer than other PDE5 inhibitors, so it is the drug of choice in patients proven non-responders to short acting ones.
DAILY USE OF PDE5 INHIBITORS

• Daily dose improves frequency, hardness, and duration of erection.
• Daily PDE5 inhibitors activate endothelial NO synthase, enhance systemic vasodilatation response that improve systemic endothelial dysfunction in patient with increased cardiovascular risk. (Rosano et al 2005)
• Daily use of PDE5 inhibitors may cause tachphylaxis. (El-Galley et al 2001)
• Currently it is unclear to develop tachphylaxis after daily use of PDE5. (Bella et al 2007)
• Proper patient counseling and follow up is necessary to overcome psychological and partner issues.
• Psychological counseling is important for successful therapy.
• Treatment of anxiety and depression.
• Awareness and treatment of female sexual dysfunction.
COMBINATION THERAPY

• Efficacy of combination therapy is encouraging.
• Combination therapy is based on etiology of ED especially associated with:
  1- LUTS.
  2- Hypogonadism.
  3- Depression.
  4- Sleep apnea.
  5- Hyperlipidaemia.
Combined PDE5 inhibitors with:

1- VED.
2- Intraurethral alprostadil.
3- ICI.
4- Androgen supplementation.
5- Alpha blockers (Doxazosin).
6- Other medications:
   - L- carnitine.
   - Atorvastin.
   - Melanocortin (Bremelanotide).
   - Pioglitazone.
   - Trazodone.
   - Pentoxifylline.
   - Vit. E.
COMBINATION THERAPY

• Caution is advised as most combination therapy studies have numerous limitations that introduce bias and low quality of evidence.

• Regardless of limitations, combination therapy provide solid foundation for future studies in complex ED management. (Robit et al 2011)
Failure of initial trial of PDE5-I

If new patient, detailed history and physical examination

Optimization of PDE5-I trial

Re-trial of same PDE5-i
- Dose escalation
- Eight attempts

Unsatisfactory response to initial PDE5-I

Evaluate for hypogonadism
- Testosterone therapy in combination with PDE5-i
  - If unsuccessful, continue testosterone therapy and proceed with trial of second PDE5-i

Patient education
- Timing
- Food and alcohol consumption
- Need for sexual stimulation

Trial of second PDE5-i
- If unsuccessful, discuss risk and benefits of alternative treatments with patient and partner

Lifestyle modification

1. Smoking cessation
2. Evaluate for hypogonadism
   - If hypogonadal, consider treatment with testosterone

   Weight loss program
   - Increased exercise

   Consider evaluation and treatment for hyperlipidemia, diabetes and hypertension

   Review and adjust medication

   Vascular surgery

   Vacuum constriction device

Daily PDE5-i
- Adjunctive measures
  - BPH treatment
  - Pioglitazone
Thank you