1. Background, definition and classification
Male erectile dysfunction (ED) (impotence) has been defined as the persistent (lasting for at least 6 months) inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. The use of validated questionnaires, such as the International Index for Erectile Function (IIEF), may be helpful in order to assess objectively not only the present status but also the impact of a specific treatment.

The overall objective of the EAU guidelines is to produce a standard for clinical evaluation and treatment, based on review of available scientific information as well as on current research and clinical practice in the field.

2. Diagnosis and work-up
The diagnosis is based on the following:
- A medical and psychological history including previous medical history in detail, surgery in the past, medication and eventual abuse.
- A disease specific history including duration and severity of the symptoms, morning erections, libido, emotional status, relationship and previous treatments against ED.
A focused physical examination focused on genito-urinary, endocrine, vascular and neurological system. A DRE should be included in patients of >50 years of age.

Laboratory test may frequently include blood glucose and testosterone estimation completed by, prolactin, prostate-specific antigen and lipid profile as indicated.

It is important that the physician facilitates communication with the patient and his partner, and explains the strategy behind the diagnostic and therapeutic approach. Often it may not be possible to involve the partner on the first visit, but an effort should be made to involve the partner during the second visit. On that occasion the physician examines the results of the blood tests. If any abnormality is observed, further investigation by referral to another specialist may be necessary. The discussion considers patient's expectations and needs, and should involve the physician, the patient and his partner. It should cover the understanding of the disorder, interpretation of the diagnostic tests and rational selection of treatment options. Patient and partner education are essential components in the management of ED.

**Specific examinations and tests**

While the majority of patients with ED can be managed within the sexual care setting, some circumstances may dictate the need for specific diagnostic testing:

- The patient with primary erectile disorder (not caused by organic disease or psychogenic disorder)
- Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery
Specific tests may also be indicated at the request of the patient or his partner
For medico-legal reasons.

Among the specific tests used are: assessment of nocturnal penile tumescence and rigidity (NTPR) using Rigiscan-NTPR; vascular studies, such as intracavernous vasoactive drug injection and duplex ultrasound completed with arteriography or cavernosometry; neurological studies, such as bulbocavernous reflex latency and nerve conduction; endocrinological studies; and a specialized psychodiagnostic evaluation. The NTPR should take place for at least two nights. The presence of an erectile event of at least 60% rigidity recorded on the tip of the penis, lasting for 10 min or more, should be considered as indicative of a functional erectile mechanism.

3. Treatment
The primary goal in the management strategy for a patient with ED is to determine the aetiology of the disease and treat it when possible. This may include correction of life-style and drug-related factors, hormone replacement, surgical reconstruction after pelvic trauma, correction of associated Peyronnie’s disease e.t.c.
When no specific therapies for ED are possible (which is for the majority of cases), a strategic approach should be followed. The patient and his partner, when possible, must be informed on the route of administration, the invasiveness, the cost and the reversibility of the treatment.
First-line therapy
Three potent selective PDE$_5$ inhibitors are currently on the market approved by the U.S. Food and Drug Administration (FDA) with proven efficacy and safety for the treatment of ED.

Oral therapy
Sildenafil (Viagra)
Sildenafil, the first PDE$_5$ inhibitor, with >20 million men treated over a 5 year post-marketing experience, is effective after 30-60 minutes in the presence of sexual stimulation but its effect is reduced by a heavy fatty meal. Dosages are 25, 50 and 100 mg: starting dose should be 50 mg and adapted according to the response and side effects.

Vardenafil (Levitra)
In vitro Vardenafil is 10-fold more potent than Sildenafil, however, this does not necessarily imply greater clinical efficacy. It is effective after 30 minutes in the presence of sexual stimulation but its effect is reduced by a heavy fatty meal. Dosages are 5, 10 and 20 mg: starting dose should be 10 mg and adapted according to the response and side effects.

Tadalafil (Cialis)
Tadalafil is effective after 30 minutes in the presence of sexual stimulation. Its efficacy is not influenced by food and alcohol. Dosages are 10 and 20 mg doses: starting dose should be 10 mg and adapted according to the response and side effects.
Table 1. Comparison of key pharmacokinetic parameters of three PDE<sub>5</sub> inhibitors, Vardenafil, Sildenafil and Tadalafil

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil (100 mg)</th>
<th>Vardenafil (20 mg)</th>
<th>Tadalafil (20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.16</td>
<td>0.75</td>
<td>2</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>3.82</td>
<td>4.7</td>
<td>17.5</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>327</td>
<td>31.8</td>
<td>378</td>
</tr>
<tr>
<td>AUC (ng/ml/h)</td>
<td>1963</td>
<td>96.3</td>
<td>8066</td>
</tr>
</tbody>
</table>

AUC: area under the plasma concentration versus time curve; C<sub>max</sub>: peak plasma concentrations; t<sub>1/2</sub>: half-life; T<sub>max</sub>: time to peak plasma concentration.

All PDE<sub>5</sub> inhibitors act in a similar way via the NO/cGMP mechanism. They are formally contraindicated in patients who take long-acting nitrates or who use short-acting, nitrate-containing medications. It may be hazardous to prescribe PDE<sub>5</sub> inhibitors in patients with: - active coronary ischaemia; - congestive heart failure and borderline low blood pressure; - borderline low cardiac volume status; - a complicated multi-drug anti-hypertensive program; - drug therapy that can prolong the half-life of PDE<sub>5</sub> inhibitors.

Table 2. Treatment-related adverse events reported by patients using the maximum dose of PDE<sub>5</sub> inhibitors, Sildenafil, Vardenafil and Tadalafil

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Sildenafil (%) (100 mg)</th>
<th>Vardenafil (%) (20 mg)</th>
<th>Tadalafil (%) (20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Flushing</td>
<td>19</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Since all 3 substances are metabolized mainly via cytochrome P450 CYP3A4, a dose adjustment should be considered when given in combination with CYP3A4 inhibitors (e.g. HIV protease inhibitors, ketoconazole, erythromycin).

In patients with hypogonadism, androgen supplementation improves erectile responses and provokes arterial cavernous dilatation.

Apomorphine sublingual (Uprima, Ixeme, Taluvian)
Apomorphine sublingual (SL) is a dopamine agonist that acts to enhance proerectile stimuli through the hypothalamic neural pathways. The sublingual formulation produces a rapid circulating plasma concentration resulting in a quick onset of action, producing an erection in a median time of 18-19 min.

**Recommended dosage**
The recommended dosages for patients with mild to moderate ED are 2 and 3 mg. It is well-tolerated and there is no interaction with other medications, food and alcohol. The main side effect is nausea in 7% of cases (also in case of a too high dosage).

**Contraindications:**
- Patients with cardiovascular conditions, or associated risk factors for cardiovascular disease, or who are on a regimen of various classes of antihypertensive medication or nitrates are at a low risk for adverse events associated with apomorphine SL
- Anatomical penile deformations (under investigation)
- Other centrally acting dopamine agents (under investigation)
Vacuum device
A vacuum device could be used in patients in stable relationships in whom the mechanism of ED is easily understood. It is also better accepted in older patients. The device applies a negative pressure to the penis, thus drawing venous blood into the penis, which is then retained by the application of a visible constricting band at the base of the penis. The adverse effects associated with vacuum therapy are penile pain, numbness and delayed ejaculation.

Psychosexual therapy
For patients with a significant psychological problem, psychosexual therapy may be given either alone or in combination with another therapeutic approach. Psychosexual therapy takes time and has been associated with variable results.

Second-line therapy
Intracavernosal injection or intraurethral therapy can be used according to the patient's wishes.

Intracavernosal injection
Several drugs have been proposed for intracavernosal injection, alone or in combination (prostaglandin E$_1$, phentolamine-vasointestinal polypeptide, phentolamine-papaverine, maxilititrimx). Patient comfort and education are essential elements of the practice of intracavernosal injection therapy. Injection therapy is effective in 60-90% of cases. The erection appears after 5-15 min and lasts according to the dose injected.
Contraindications

- Hypersensitivity to the drug employed
- In men at risk of priapism.

Side effects

Side-effects include prolonged erections or priapism, penile pain and fibrosis.

Treatment of priapism

After 4 h of erection, patients are advised to consult the doctor to avoid any damage to the intracavernous muscle, which would provoke permanent impotence. A 19-gauge needle is used to aspirate blood and therefore to decrease the intracavernous pressure. This simple method is usually sufficient to make the penis flaccid. However, if the penis becomes rigid again after this, phenylephrine intracavernous injection at a dose starting at 200 µg every 5 minutes and increasing to 500 µg if necessary. The risk of having a prolonged erection during following subsequent injections cannot be predicted. When this problem occurs, the dose is usually reduced for the next injection. The patient must be carefully observed for systemic effects of the treatment used.

Intraurethral therapy

Prostaglandin $E_1$ may be administered intraurethrally in the form of a semi-solid pellet. A band placed at the base of the penis seems to improve the resulting rigidity. About 70% of patients have been satisfied or very satisfied. Side-effects include penile pain and hypotension, and the clinical success rate is lower than that achieved with intracavernosal therapy.
Third-line therapy
Prosthesis
For patients who fail pharmacological therapy or who prefer a permanent solution to their problem, surgical implantation of a prosthesis may be considered.
Two types of prosthesis exist: malleable and inflatable. The inflatable penile prosthesis provides not only a more cosmetic erection but also a more satisfying one. Penile growth is usually better with an inflatable rather than a semi-rigid erection, although the former is associated with an increased rate of mechanical failure and complications.

Side effects
Prosthetic infection is the most problematic complication following surgery as the combination of infection and a foreign body requires removal of the prosthesis. The patients most commonly affected by infection problems are diabetics.

Surgical implantation of a prosthesis should only be performed in centres with a special interest in this field.

4. Conclusion
It must be emphasized that the physician should warn the patient that sexual intercourse is considered to be a vigorous physical activity, which increases heart rate as well as cardiac work. Physicians should assess the cardiac fitness of patients prior to treating ED.

An increasing number of oral agents have been introduced for the pharmacological treatment of ED with very good success rates. However, any successful pharmacological treatment for
erectile failure demands a degree of integrity of the penile mechanisms of erection.

Clinical trials performed in multiple countries have shown strong efficacy and good safety of PDE$_5$ inhibitors in the general populations as well as in a difficult to treat population such as patients with diabetes mellitus and as patients having undergone a post-radical prostatectomy. There have been no published head to head clinical trials comparing Sildenafil, Vardenafil and Tadalafil.

Patients should be encouraged to try all PDE$_5$ inhibitors and develop their own opinion. They will choose the compound that is perceived by them to have the best efficacy as well as other features such as time of onset, duration of action, window of opportunity and their own individual experience with side effects.

Apomorphine in post-marketing studies seems to be effective mainly in patients with psychogenic and a mild organic impotence and should be reserved in patients contraindicated for PDE$_5$ inhibitors.

This short booklet is based on the more comprehensive EAU guidelines (ISBN 90-806179-8-9), available to all members of the European Association of Urology at their website - www.uroweb.org.