Oral Drug Therapy for Erectile Dysfunction: Overview and Aeromedical Implications

Alon Grossman, Erez Barenboim, Bella Azaria, Yaniv Sherer, and Liav Goldstein


Approximately 150 million men worldwide experience erectile dysfunction, whereby they are unable to maintain an erection adequate for satisfactory sexual performance. This population is projected to more than double in the next 25 yr. Introduction of the phosphodiesterase inhibitors has revolutionized the management of this common problem, encouraging many more men to seek treatment. The issue of erectile dysfunction treatment is a growing concern in the aviation community as well. This is particularly relevant in civil aviation, as this population is older and has co-morbidities that may contribute to the development of erectile dysfunction. In this article we will review the available options for oral treatment of erectile dysfunction and discuss implications regarding their use in aviators based on the information available in the literature.

Keywords: aerospace medicine, aviators, erectile dysfunction, sildenafil, tadalafil, vardenafil.

APPROXIMATELY 150 MILLION men worldwide are unable to achieve and maintain an erection adequate for satisfactory sexual performance. Consistent with the increasing life expectancy of the general population, it is projected that this population will more than double in the next 25 yr (7). The introduction of phosphodiesterase inhibitors for the treatment of this common problem has revolutionized the ease of treatment and the population’s compliance. Military aviators usually comprise a relatively young population in which the magnitude of erectile dysfunction is negligible, yet this problem is not uncommon in commercial pilots. This community consists of older pilots who may suffer from general medical conditions, such as diabetes mellitus and hypertension that may contribute to a greater frequency of erectile dysfunction. Thus, questions regarding the use of phosphodiesterase inhibitors for erectile dysfunction in aviators are constantly presented to flight surgeons. This review will present the current available options for the oral treatment of erectile dysfunction and their side effects. We will attempt to set recommendations for the flying community regarding the use of phosphodiesterase inhibitors based on the data available in the literature.

Pathophysiology of Erectile Dysfunction and Basis for Treatment

Penile erection is a hemodynamic process that depends on the complex interaction between the nervous system and the vascular system. This interaction eventually results in smooth muscle relaxation and vasodilatation in the corpora cavernosa (1,2). Sexual stimulation leads to the release of nitric oxide, which promotes production of cyclic GMP (cGMP) via the cytosolic enzyme guanylate cyclase. This substance decreases intracellular calcium, thereby allowing relaxation of the smooth muscle cells in the cavernosal bodies. Penile blood flow increases and sinusoidal spaces expand, preventing venous outflow of blood and resulting in erection (6). Any factor, being psychological, hormonal, vascular, or cavernosal, which disrupts this sequence, may result in erectile dysfunction (ED).

Phosphodiesterase (PDE) enzymes are widely distributed throughout the body and 11 families of these enzymes have been identified in human tissues. Degradation of cGMP in cavernosal tissue, which terminates erection, is catalyzed primarily by PDE5. Most oral agents available for ED treatment work through the selective inhibition of PDE5. These agents increase cellular cGMP concentrations in the corpora cavernosa, thereby amplifying smooth muscle relaxation and vasodilatation (9). These agents help to maintain the erectile response to sexual stimuli and do not produce an erection in the absence of sexual stimulation with consequent nitric oxide release. This class comprises 3 agents that are currently approved for the treatment of ED—sildenafil, tadalafil and vardenafil. Their mechanism of action is similar, though they differ in pharmacokinetic properties (10) and known side effects. The differences between the available agents are presented in Table I.

Pharmacodynamics and Clinical Efficacy

Sildenafil (Viagra®) is the first agent developed in this class, and, therefore, the best studied. For most patients,
the recommended dosing regimen is 50 mg taken on an as-needed basis approximately 1 h prior to sexual activity. Based on patient response, this may be decreased to 25 mg or increased to the maximum dose of 100 mg (19). The drug is 96% bound to plasma proteins and is cleared predominantly by the liver. Drug accumulation following repeated once-daily dosing is negligible. The drug is 10 times more potent in the inhibition of PDE5 compared with PDE6.

Various studies demonstrated a significant improvement in both the ability to attain an erection and the ability to maintain an erection in those treated with sildenafil as compared with placebo (3,13). This improvement persisted regardless of patient population and was present in all causes of ED, including diabetes mellitus, hypertension, peripheral vascular disease, following urologic procedures, and depression. In long-term follow-up at 1 yr, 2 yr, and 3 yr, over 95% of the patients had improved erections and an improved ability to engage in sexual activity. A phase 2, multi-center, randomized, double-blind, parallel trial compared tadalafil (Cialis®) with placebo in 179 men aged 21 to 72 yr with over 3 mo duration of ED. All tadalafil doses (2, 5, 10, and 25 mg) were associated with significant improvements in erectile function as compared with placebo (12). Overall satisfaction with the sexual experience was up to 58.7% in treated subjects (16.6% in placebo) and up to 99.6% in placebo. Tadalafil was found to be effective for up to 36 h following treatment (15).

Vardenafil (Levitra®, Nuviva®) at varying doses (5, 10, or 20 mg) significantly improved measurements of sexual function and satisfaction. In general, efficacy responses were dose-related with patients receiving 20 mg showing the greatest improvements (16). The efficacy of vardenafil was independent on patient population (17). Vardenafil’s plasma levels are negligible after 24 h and hence its length of action is intermediate between the other two agents (18).

### TABLE 1. COMPARISON OF CLINICAL CHARACTERISTICS OF SILDENAFIL, TADALAFIL AND VARDENAFIL.

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Tadalafil</th>
<th>Vardenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 (h)</td>
<td>4</td>
<td>17.5</td>
<td>4.2</td>
</tr>
<tr>
<td>PDE1/PDE5 selectivity</td>
<td>1:80</td>
<td>1:1000</td>
<td>1:130</td>
</tr>
<tr>
<td>PDE2/PDE5 selectivity</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
</tr>
<tr>
<td>PDE3/PDE5 selectivity</td>
<td>1:4000</td>
<td>1:1000</td>
<td>1:1000</td>
</tr>
<tr>
<td>PDE4/PDE5 selectivity</td>
<td>1:1000</td>
<td>1:1000</td>
<td>1:1000</td>
</tr>
<tr>
<td>PDE6/PDE5 selectivity</td>
<td>1:10</td>
<td>1:700</td>
<td>1:15</td>
</tr>
<tr>
<td>Headaches</td>
<td>10%</td>
<td>4.8%</td>
<td>6.8-15.3%*</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6%</td>
<td>3.4%</td>
<td>0.7-6.7%*</td>
</tr>
<tr>
<td>Flushing</td>
<td>9%</td>
<td>2.7%</td>
<td>10.2-11.3%*</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>3%</td>
<td>&lt;0.1%</td>
<td>0.1-1%*</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>6.5%</td>
<td>4.1%</td>
<td>2.8-7.3%*</td>
</tr>
</tbody>
</table>

Adapted with permission from American Journal of Cardiology (19).

*Dose-related.*

### Side Effects

**Sildenafil:** The most common adverse events in clinical trials of sildenafil have included headaches, flushing, and nasal congestion. These side effects are due to the drug’s vasodilator effects. Dyspepsia is an additional common side effect, and is probably secondary to relaxation of the lower esophageal sphincter, whose integrity is partially maintained by PDE5. Morales reviewed the spectrum of side effects from flexible-dose sildenafil (8). Headaches (1.1%), flushing (0.4%), and nausea (0.4%) were the most common adverse events leading to discontinuation of treatment during flexible-dose treatment. During fixed-dose regimens, the most common treatment related side effects were dose-related, being higher at 100 mg compared with 25 or 50 mg dosing (14). Reports of priapism associated with the use of sildenafil in healthy subjects are anecdotal (23).

Abnormal vision is a rare cause of treatment withdrawal. PDE6 has a role in the phototransduction process. Studies in dogs have demonstrated that sildenafil produces a dose-related reversible effect on hyperpolarization of retinal tissue in response to light, consistent with inhibition of PDE6. Long-term studies in animals demonstrated no functional or morphologic alteration of the retina or optic pathway (11). Acute exposure studies have been performed in humans and the only effect found was a transient difficulty in discriminating blue-green hues (11). Clinically, this was reported as abnormal vision in 3% of patients receiving 100 mg flexible-dose treatment. This may increase to 11% in those taking 100 mg fixed-dose regimens (14) and up to 40% in those taking 200 mg (11). A small long-term study in a cohort of patients performed over 1 yr did not demonstrate any abnormalities of visual function.

Cardiovascular effects of sildenafil raised particular interest and effects of this treatment on cardiovascular hemodynamics were examined using Swan-Ganz catheterization that was followed by 40 mg of sildenafil injected intravenously. This dose is equivalent to a dose 2-5 times higher than a 10-mg dose. The results demonstrated a mild decrease in mean resting systolic (7%) and diastolic (10%) pressures, right atrial pressure (28%), pulmonary artery pressure (28%), pulmonary wedge pressure (20%), and cardiac output (7%); however, the normal hemodynamic response to exercise was preserved (4). Another study examined the effects of sildenafil on cardiopulmonary responses during stress and concluded that young healthy men without signs of systemic atherosclerosis compensate well for the vasodilatatory effect of sildenafil during exercise, while in older patients with vasculogenic erectile dysfunction, moderate changes may be noted (22). Sildenafil therapy does not appear to be associated with ischemic events either at the time of introduction of therapy or during long-term use and sildenafil does not interact in a potentially hazardous way with anti-hypertensive or anti-anginal therapy, with the exception of nitrates (24). As might be expected from the impact of sildenafil on the nitric oxide-cGMP system, it may potentiate the hypotensive effects of nitrates.
Therefore, use of all forms of nitrates is contraindicated in patients taking sildenafil.

**Tadalafil:** Headache, dyspepsia, and back pain were the most common adverse effects reported in phase 2 placebo-controlled trials. Additional adverse events reported included nasal congestion (4.1%) and flushing (2.7%). Tadalafil is 700–1000 times more potent for the inhibition of PDE5 compared with PDE6 and thus was expected to cause much less visual abnormalities. Indeed, visual abnormalities were reported in less than 0.1% of those treated with tadalafil (19). Daily administration of tadalafil 20 mg for 26 wk in healthy male subjects or patients with mild erectile dysfunction resulted in BP changes similar to those observed after placebo administration (5). Simultaneous use of tadalafil and nitrates is contraindicated.

**Vardenafil:** Headache, flushing, dyspepsia, and nasal congestion were the most common adverse events reported during treatment with vardenafil. Side effects were generally dose-related. This agent is more selective to PDE5 as compared with sildenafil, but is much less selective than tadalafil (approximately 15 times more potent for the inhibition of PDE5 as compared with PDE6). Therefore, the visual side effects reported were at a rate of 0.1–1%. Most adverse events reported were mild or moderate (19). Again, simultaneous use of this agent with nitrates is contraindicated.

**Aeromedical Considerations**

The extent of use of oral agents for erectile dysfunction by aviators is unknown and has not been reported in the literature. In future years, the use of these agents will greatly increase in the aviation community in parallel with the increase in use in the general population. General aviation pilots are usually older and may suffer from co-morbid conditions; therefore, erectile dysfunction is more prevalent in this population. Military aviators are usually younger, where erectile dysfunction is uncommon. Therefore, the population most likely to consult flight surgeons regarding the use of these agents is the commercial aviation community. Yet, military aviators may continue to fly well into their forties, where the magnitude of erectile dysfunction rises significantly and questions regarding the use of PDE5 inhibitors may be raised to the military flight surgeon as well. It is important to note that no studies were conducted regarding the side effects of these agents in the flight environment and the position stated in this paper is based on data gathered in non-flying personnel.

The association between ED and cardiovascular disease is of particular concern to the flight surgeon. Speel et al. found that in patients in the 50–59-yr-old age group, those with cavernous artery insufficiency had a significantly elevated risk to develop coronary heart disease. No significant difference in coronary heart disease risk was noted in the 40–49-yr-old group or in the 60–69-yr-old group (21). Additional studies supported the association between ED and coronary heart disease risk (20). We believe that a complaint of ED in an aviator of any age should raise concern regarding the potential for coronary heart disease. In such patients a thorough search for modifiable risk factors should be conducted and a higher frequency of non-invasive coronary evaluation should be considered based on clinical features and additional risk factors.

Following exclusion of coronary heart disease and treatment of modifiable risk factors, the potential side effects of the treatment should be considered. As mentioned above, most side effects experienced with the treatment were mild to moderate and did not result in treatment withdrawal. Headaches may be troublesome, but are usually of short duration and respond well to analgesics. Dyspepsia may worsen on exposure to gravitational forces but, as mentioned above, is usually mild and transient.

Rhinitis was reported in a small number of patients following fixed-dose regimens of sildenafil and at lower rates during treatment with tadalafil and vardenafil. This may contribute to barotrauma in jet fighter and commercial pilots. The potential for this side effect should be emphasized to the aviator prior to the beginning of treatment and he should be warned about the dangers of flying with nasal congestion. The lower rate of nasal congestion during tadalafil treatment is probably due to this drug’s greater selectivity for PDE5. Vardenafil has medium selectivity for PDE5 and rhinitis was reported with this drug. The lower rate of nasal congestion during treatment with these agents makes them particularly attractive for aviators, in whom the development of nasal congestion may impair mission completion.

The visual complaints reported with the use of sildenafil may distract the aviator. The clinical significance of these visual disturbances has not been evaluated thus far and such studies should be undertaken in order to evaluate this issue.

Current FAA regulations regarding the use of sildenafil allow use of this agent, provided a period of 6 h has elapsed following the last dose before the aviator returns to the cockpit. We believe that the greater selectivity of tadalafil for PDE5, the extremely low rate of visual complaints and the lower rate of nasal congestion in tadalafil-treated patients, make this agent the preferred treatment for ED in aviators. Despite the longer half-life of this agent, we believe that the lower rate of complications reported with the use of tadalafil makes this drug an attractive option for use in aviators. We also believe that use of sildenafil and vardenafil should be more prudent and aviators should avoid flying while under the influence of these agents (6–8 h for sildenafil and up to 24 h for vardenafil). In order to evaluate the effects of PDE5 inhibitors in high-performance environments, we recommend further tests be conducted including various visual tests and in-flight monitoring of heart rate and BP.

**SUMMARY**

The use of oral agents for the treatment of ED is predicted to increase substantially in the coming years. This will certainly result in a greater consumption rate in aviators as well. The appearance of ED in aviators should first raise concern regarding potential coronary heart disease. Present data support the use of tadalafil as the preferred agent of treatment among aviators,
because of its negligible effects on vision and the lack of report of rhinitis. The use of sildenafil and vardenafil should be more prudent because of the unknown impact of their visual side effects and because of their potential to cause rhinitis, which may contribute to barotrauma. Further studies are required to evaluate the potential side effects of these agents in the high-performance flying environment.

REFERENCES