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A Risk-Benefit Assessment of Sildenafil in the Treatment of Erectile Dysfunction

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Contents

Abstract

Sildenafil is an oral treatment for erectile dysfunction (ED). It acts as an inhibitor of 3′,5′-cyclic guanosine monophosphate-phosphodiesterase type 5. An effective treatment for ED is required to produce an erectile response sufficient for satisfactory sexual performance. This has been documented for sildenafil in men with ED of differing aetiologies and baseline severity in various types of clinical trials.

Sildenafil treatment is characterised by a good tolerability profile and low treatment discontinuation rate caused by treatment-related adverse effects. Most of the adverse effects associated with sildenafil are extensions of the pharmacological action of the drug. There is no significant difference in the adverse effect profile (headache, flushing, dyspepsia, nasal congestion and abnormal vision) of this agent as assessed by clinical data obtained either in the pre- and postlaunch periods. Because of its acceptable risk-benefit ratio, sildenafil can be prescribed to a very large group of patients with ED. The reports of serious cardiovascular events associated with the use of sildenafil (including anecdotal reports of deaths) have been very thoroughly analysed. A number of studies have not shown any difference in the risk of serious cardiovascular events in sildenafil- and placebo-treated patients. However, when making a risk-benefit evaluation, certain subgroups of patients need to be considered separately. In particular, sildenafil is contraindicated in patients receiving nitrate therapy. In some other subgroups of patients, the risks and benefits of treatment need to be assessed on an individual

basis and it is hoped that additional data will clarify any possible risks associated with sildenafil administration such patients.

It is helpful to compare the risk-benefit profile of sildenafil with the characteristics of other oral drugs for ED. According to the preliminary data, apomorphine and phentolamine are possible future options for the treatment of ED; however, there needs to be further clinical evaluation of these agents. Initial data have shown that sildenafil can be successfully combined with intracavernosal injection in patients nonresponders to either therapy.

In conclusion, favourable characteristics make sildenafil suitable for the first-line therapy for a substantial proportion of patients with ED.

Erectile dysfunction (ED), previously referred to as impotence, is the consistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance.[1] The problem is very common, age-related and according to the Massachusetts Male Aging Study (MMAS), conducted from 1987 to 1989, the combined prevalence of minimal, moderate and complete ED in men aged between 40 to 70 years was 52%.[2] The results of the MMAS showed that risk factors for ED are: cardiovascular disease (heart disease, hypertension, low serum high density lipoprotein levels); diabetes mellitus; medication use (drug-induced ED); cigarette smoking; psychological factors; and depression.[2,3]

Nitric oxide plays the principal role in the process of penis erection. Nitric oxide promotes the activation of a second messenger molecule, 3′,5′-cyclic guanosine monophosphate (cGMP).[4,5] An increased intracellular cGMP level is associated with a reduction in cytosolic calcium and leads to the relaxation of corporeal smooth muscle cells which is necessary for penile erection.

Sildenafil is a new drug for the peroral treatment of ED that acts as a selective inhibitor of cGMP phosphodiesterase type 5 (PDE5).[6,7] After the drug was approved by the US Food and Drug Administration (FDA) in March 1998, sildenafil attracted enormous attention from the medical profession and the lay public because of the nature of the disease, the fact that sildenafil was the first effective and simple treatment for ED and because of reports of serious adverse effects.

This review is a risk-benefit assessment of sildenafil treatment. The literature identification was performed as a 2-step procedure. The first step included a Medline search of articles published since 1996 (the year of the first published articles on sildenafil and ED). The key words used in the search were: sildenafil, erectile dysfunction, impotence. The second step was a 'hand search' of the available publications, mostly based on examination of reference lists from articles found on Medline. Additional data were also acquired through a search of various internet sites. The analysis of the data, especially considering the efficacy and safety of the drug, was performed with the aim of obtaining up-to-date information concerning sildenafil usage in different subgroups of patients with ED.

1. Benefits of Treatment

The benefits of sildenafil treatment, according to the above definition of ED, are an erectile response sufficient for satisfactory sexual performance in patients with ED. The efficacy of the drug has been documented in men with ED of differing aetiology and baseline severity in various types of clinical trials.[6,8-14] Different methods for quantifying the efficacy of sildenafil efficacy have been used in different studies. One of the most popular and most widely used is International Index of Erectile Function (IIEF).[15] The test is a self-administered assessment consisting of a 15-item questionnaire. According to the questions, 5 domains of male sexual function could be analysed (erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction).[15] Besides IIEF, a global efficacy question (an answer of yes to the

Table I. Results of demonstrating the efficacy of sildenafil in patients with erectile dysfunction (ED) of differing aetiology. Sildenafil dose was adjusted according to efficacy and tolerability (25, 50 or 100mg) in all studies, but in the spinal cord injury study[13] the dose was fixed at 50mg

Cause of ED	Study design	No. of study participants		Efficacy (%)[a]		Reference
		Sildenafil	placebo	Sildenafil	placebo	
Different causes	r, db, pc	163	166	74	16	9
Type 1 diabetes mellitus	r, db, pc	22	28	55	19	10
Type 2 diabetes mellitus	r, db, pc	144	104	57	8	10
Ischaemic heart disease	retro[b]	213	102	70	20	11
Cardiovascular disease	r, db, pc	136	88	71	24	12
Spinal cord injury	r, db, pc	13	14	75	7	13
Diabetes mellitus	o, nc	36	0	58	0	14
Neurological	o, nc	9	0	56	0	14
Prostate surgery	o, nc	77	0	35	0	14
Psychogenic	o, nc	9	0	89	0	14
Vasculogenic	o, nc	43	0	86	0	14
Peyronie's disease	o, nc	7	0	71	0	14
Unknown	o, nc	86	0	81	0	14

a Efficacy measurements represent a positive (yes) answer to a global efficacy question (GEQ) [all studies] and the percentage of satisfied patients according to an abbreviated version of International Index of Erectile Dysfunction (IIEF), [reference 14] which includes 5 questions regarding sexual function. The outcome was defined as a satisfaction level of 4 or 5 on a 5-point scale.[14]

b Retrospective, subgroup analysis of 9 randomised, double-blind, placebo-controlled studies.

db = double-blind; **nc** = noncomparative; **o** = open; **pc** = placebo-controlled; **r** = randomised.

global efficacy question: 'Did the treatment improve your erections?'), a diary or log of erectile activity and a partner questionnaire about the erection during sexual activity have also been used.[8,9] Table I is a summary of sildenafil efficacy in men with ED of various aetiologies. Significant efficacy is obvious in all patient groups while the variability of efficacy can be based on aetiologies.

In an open, uncontrolled study involving 308 consecutive patients in clinical practice, Jarow et al.[14] observed a significant disparity in the overall rate of satisfaction seen in patients in whom the cause of ED was diabetes mellitus, neurological disorders or prostate surgery versus those with ED of vasculogenic or psychogenic origin. An explanation for this could lie with the mechanism of action of sildenafil for which an adequate nerve supply to the corpora is more important than the blood flow.[14] Two recent studies performed in patients after radical prostatectomy confirmed that the degree of nerve sparing has a significant impact on sildenafil efficacy, i.e. a better response rate to the drug was observed in patients who underwent nerve sparing procedures.[16,17]

2. Adverse Effect Profile

Treatment with sildenafil is associated with a very low withdrawal rate because of treatment-related adverse effects, according to the results in clinical trials.

In an open-label study of 32 weeks' duration by Goldstein et al.[8] the withdrawal rate because of adverse effects was <2% (4 of 225 men). In a 12-week, randomised, double-blind, placebo-controlled study by Padma-Nathan et al.[9] the withdrawal rate because of adverse effects was very similar at 1.8% (3 of 163 men). Morales et al.[18] pooled the results of 11 flexible-dose, placebo-controlled studies of sildenafil taken when required, and the overall rate of withdrawal as a result of adverse effects was comparable for patients in the sildenafil (2.5%) and placebo (2.3%) treatment groups. In 10 open-label studies of sildenafil that enrolled 2199 patients over a 1-year period 2% of patients withdrew because of adverse effects and 4% withdrew because of lack of efficacy.[18] In these 10 open-label studies the most common adverse effects were:

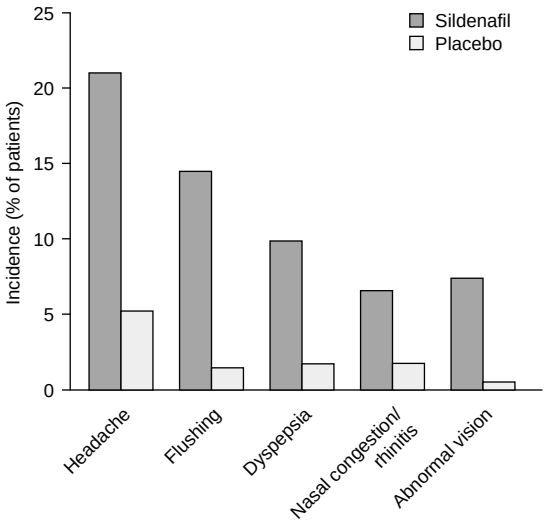

Fig. 1. Incidence of adverse effects for sildenafil (n = 2340) and placebo (n = 1332) as recorded in 11 placebo-controlled studies.[11]

- headache (10% of patients)
- flushing (9%)
- dyspepsia (6%)
- respiratory tract infection (6%)
- abnormal vision (2%).

The overall incidence of adverse effects for sildenafil and placebo recorded in 11 placebo-controlled studies[11] is summarised in figure 1.

The incidence of the adverse effects has been shown to increase with dosage showing that these adverse effects are dose dependent (fig. 2). This has been confirmed in 2 representative, multicentre, randomised, double-blind, placebo-controlled, fixed-dose studies (sildenafil 25, 50 or 100mg or placebo) performed in the US (n = 532)[8] and Europe (n = 514).[19]

It should be emphasised that the adverse effects seen in clinical trials were usually transient and mild and lasted a few minutes to a few hours following drug administration.[8,9,18] The analysis performed by Morales et al.[18] of flexible-dose, placebo-controlled studies of sildenafil used on an as needed basis showed that of the 574 adverse effects experienced by patients treated with sildenafil, 7% were severe, and of the 350 adverse effects experienced by placebo-recipients, 9% were severe. These 5 most common adverse effects are direct extensions of the pharmacological action of sildenafil (intrinsic adverse drug effects). It is also important to mention that the profile of the most common adverse effects (fig. 1) is the same as that seen in clinical trials conducted since the drug was launched.[14,17,20,21]

The first study assessing the safety and efficacy of sildenafil in postmenopausal women with sexual dysfunction revealed a similar adverse effect profile to that seen in men, with the exception of clitoral discomfort and 'hypersensitivity', in that occurred in 7 women (21%).[22]

2.1 Headache, Flushing, Dyspepsia and Nasal Congestion

Four of the most common adverse effects are headache, flushing, dyspepsia and nasal congestion and the pharmacodynamic explanation for these effects is the inhibition of PDE5 by sildenafil. Headache and flushing are the result of peripheral vasodilatation.[23] Headache was the most frequent adverse event to cause discontinuation of sildenafil treatment in fixed-dose studies (0.6% in the 100mg sildenafil group).[18] In as needed, flexible-dose studies, the treatment discontinuation rates for the 3 most common adverse effects were: headache 1.1%, flushing 0.4% and nausea 0.4%.[18]

Hyperaemia of the nasal mucosa related to PDE5 inhibitory effect of sildenafil in blood vessels leads to nasal congestion.[7] Dyspepsia could be attributable to the inhibition of PDE5, because of its role in maintaining the integrity of the gastrointestinal junction.[7] Furthermore, this potentially positive effect of sildenafil on the oesophageal musculature, was tested in 14 patients with idiopathic achalasia.[24] The results of this study showed a significant decrease in lower oesophageal sphincter tone, residual pressure, and wave amplitude after sildenafil treatment (50mg) in comparison with the results achieved in basal period and in the placebo group. A marked interpatient variability was observed with maximum inhibitory effect occurring 15 to 20

minutes after the drug application and lasting for less than 1 hour.

2.2 Abnormal Vision

Abnormal vision is characterised by transient alteration in colour vision and hue, increased sensitivity to light or blurred vision.[8,10,11,18,25,26] Sildenafil causes this phenomenon by inhibiting PDE6 which is localised in the retina. PDE6 plays a key role in light signal transduction and 10 times higher concentrations of sildenafil are needed to inhibit PDE6 in the retina [50% inhibition rate (IC_{50}) = 34 to 38 nmol/L] than PDE5 in the corpus cavernosum (IC_{50} = 3.5 nmol/L).[7,27] The visual effects of sildenafil at various doses (50, 100 and 200mg) have been tested in healthy volunteers.[28] The only changes from baseline were in colour discrimination (blue-green) scores and these changes were dose related. The colour discrimination impairment was observable from 1 to 3 hours after sildenafil therapy. Following treatment with sildenafil there were no differences between the results of visual tests performed in healthy volunteers and in patients with diabetic retinopathy.[28]

2.3 Cardiovascular

In November 1998, considerable medical concern was caused by the fact that the FDA announced that it had received 130 reports of deaths potentially related to sildenafil use in the period from sildenafil approval in March 1998 to mid-November 1998.[29] In this time 6 million prescriptions had ben written for sildenafil. 77 of the 130 reports related to probable cardiac events. According to the FDA report, 44 of the cardiovascular deaths could have been temporally connected with sildenafil use

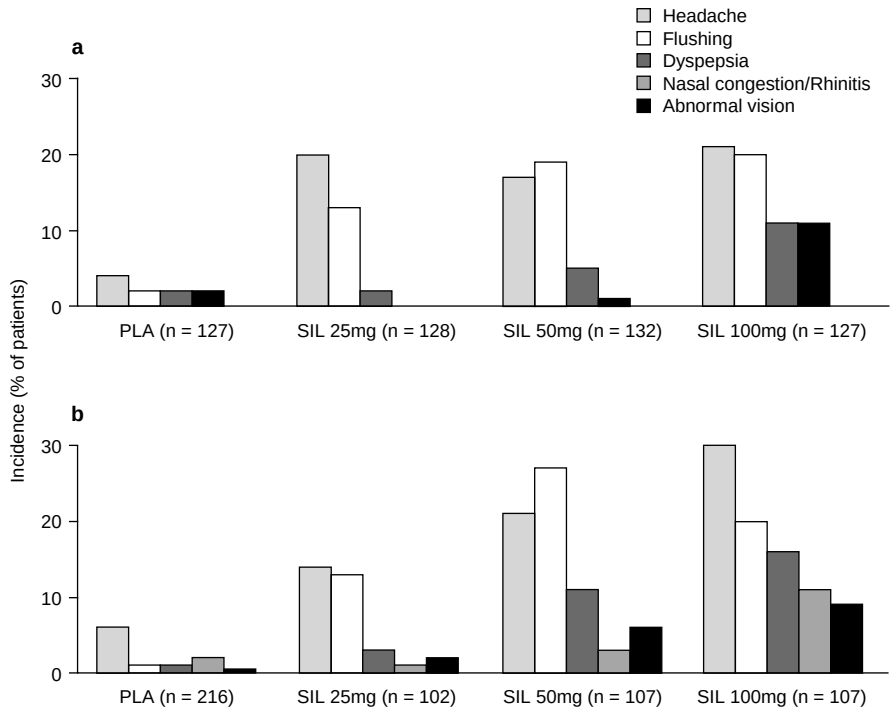

Fig. 2. Incidence of adverse effects of with fixed-doses of oral sildenafil for the treatment of erectile dysfunction of various aetiologies from 2 placebo-controlled studies: (**a**) Montorsi et al.[19] and (**b**) Goldstein et al.[8] **PLA** = placebo; **SIL** = sildenafil.

and occurred within 4 to 5 hours following drug ingestion (including 27 deaths that occurred during or immediately after sexual intercourse). Further analyses were performed because it was difficult to draw exact conclusions from the FDA data because of the known limitations of the FDA spontaneous postmarketing adverse events reporting system. The result of these analyses was the expert consensus document produced by the American College of Cardiology (ACC) and American Heart Association (AHA) in January 1999.[30,31] An analysis of the incidence of serious cardiovascular adverse events (the rate of myocardial infarction) showed that the incidence of such events was similar for the sildenafil (>3700 patients) and placebo (almost 2000 recipients) groups in phase II/III studies.[30,31] Any analysis of serious cardiovascular adverse events seen in the postmarketing period should take into account the fact that the incidence of ED and cardiovascular disease increases with the age and they have 1 or more risk factors in common (e.g. hypertension, hypercholesterolaemia, cigarette smoking, diabetes mellitus).[2,32-35] Therefore, according to epidemiological data of cardiovascular mortality in the US, anecdotal reports of deaths potentially associated with sildenafil treatment could be expected.[32-35] Preliminary results based on prescription event monitoring in the UK on the cohort of 5391 men confirmed that according to the age-standardised mortality and morbidity rates, there is no evidence of an increased risk for myocardial infarction or ischaemic heart disease between the sildenafil recipients and the general population of men.[36] Because it is possible that the interaction between sildenafil and nitrates was the cause of some of the lethal events, the first recommendation of ACC/AHA expert consensus document was to point out that it is absolutely contraindicated to use sildenafil and nitrates (e.g. nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, other organic nitrates and illicit substances containing organic nitrates – also called 'poppers' such as amyl nitrate or nitrite) concomitantly.[30,31] Since this contraindication was known at the time the clinical trials in phase II/III were conducted, patients taking nitrates were not included in these studies. Sildenafil, taken together with nitrates, could intensify the development of clinically significant hypotension.[37,38] Hypotension is a possible cause of the deaths that occurred in patients with cardiac disease who took sildenafil.[33,34,37,38] Other possible causes for the fatalities are: an increased heart oxygen demand during sexual activity; cardiac arrhythmias induced by sildenafil or sexual activity; or a combination of different causes.[34,38-40] The ACC/AHA recommendations for safer prescribing of sildenafil to patients with cardiac disease are included in table II.

Two recent studies are in concordance with the results of the analyses of serious cardiovascular adverse events that have occurred since the drug was marketed. Olsson and Persson[12] evaluated the efficacy and safety of sildenafil for the treatment of ED in patients with cardiovascular disease. This study and the study of Conti et al.[11] (in patients with ischaemic heart disease) confirmed that sildenafil is a well tolerated treatment for patients with cardiovascular disease who do not take nitrate therapy.

3. Sildenafil Versus Other Drug Treatments

An 'ideal' drug for ED treatment should be safe and effective, reversible, mimic natural erections, produce predictable and consistent responses and should be administered orally, when required.[42] These characteristics could be helpful when comparing sildenafil with other erectogenic agents. Because of its favourable characteristics, sildenafil is considered the first-line therapy for patients with ED.[42] Other oral agents that are available for the treatment of ED are:

- yohimbine
- trazodone
- apomorphine
- phentolamine.

Yohimbine is a selective α_2-adrenoceptor antagonist with contradictory results in ED treatment.[43,44] The drug was not effective at a high oral dose (100mg) in a group of patients with ED of mixed

Table II. Recommentations for appropriate sildenafil use in different subgroups of patients with erectile dysfunction

Patients in whom caution is required when prescribing sildenafil[a]
Patients with active coronary ischaemia who do not take nitrates (e.g. patients with a positive exercise test for ischaemia)[30,31]
Patients with congestive heart failure and borderline low blood pressure and borderline low volume status[30,31]
Patients taking a complicated, multidrug, antihypertensive programme[30,31]
Patients taking drugs that can prolong the half-life of sildenafil (i.e. inhibitors of cytochrome P450)[30,31]
Patients who have had a myocardial infarction, stroke or life-threatening arrhythmia within the last 6 months[41]
Patients with resting hypotension (BP <90/50mm H) or hypertension (BP >170/110mm Hg)[41]
Patients with retinal genetic phosphodiesterase defect[26]
Patients with bleeding disorders and patients with active peptic ulceration[41]
Patients with anatomical deformations of the penis[41]
Patients with predisposition to priapism (e.g. leukaemia, multiple myeloma, sickle cell anaemia)[41]
Patients at in whom sildenafil is contraindicated[b]
Concurrent use of nitrates[30,31] or nitric oxide donors

a The risk-benefit ratio depends on assessment of the individual patient. There is a lack of controlled clinical data on the use of sildenafil in these patients and further research is required.

b The risk-benefit ratio not acceptable in these patients.

BP = blood pressure.

aetiology and in patients with organic ED.[45,46] According to the results of a trial by Montorsi et al.[47], yohimbine was effective only in patients with ED of psychogenic origin when given in combination with trazodone. In a meta-analysis of 7 trials, Ernst and Pittler[48] demonstrated that the efficacy and safety of yohimbine is superior to placebo in the treatment of ED. The safety profile seems to be acceptable.[48] There is a need for further studies in order to prove the place of the drug in ED treatment.

Trazodone is a second generation antidepressant associated with a number of adverse effects (e.g. drowsiness, dizziness, insomnia, headache and bodyweight loss), which are not acceptable for a treatment for ED.[49] In addition, the efficacy of trazodone in ED has been shown to be not much better than placebo.[50,51]

Apomorphine, formulated as sublingual tablets for controlled absorption, showed an erectogenic potential in patients with psychogenic ED.[52] In the selected group of patients (those with no organic cause of ED), apomorphine, at a dose of 3 or 4mg, produced significantly durable erections in 67% of individuals (8 of 12 patients).[52] More extensive clinical studies should confirm the efficacy and safety of apomorphine, specially considering that significant nausea is the main adverse effect of this agent.[52] The drug is in phase III clinical trials.

Phentolamine-induced erections are the result of competitive α_1- and α_2-blockade and also by indirect functional antagonism via a non-adrenergic, endothelium-mediated mechanism, which involves nitric oxide synthase activation.[43,44,53] The efficacy of oral phentolamine treatment in patients with ED has been confirmed in a number of studies.[54-56] The study of Becker et al.[56] in 40 patients showed that full erections were achieved in 2 of 10 patients treated with placebo, 3 of 10 patients treated with phentolamine 20mg, 5 of 10 patients treated with phentolamine 40mg and 4 of 10 patients treated with phentolamine 60mg. Only one minor adverse effect was observed in 1 patient treated with phentolamine 60mg. A head-to-head comparison of oral phentolamine and sildenafil will be possible after the presentation of the drug approval documentation for phentolamine.

It is obvious that all 4 of the oral agents discussed here require further study of their efficacy and safety in order for an adequate comparison with sildenafil to be made. Of particular interest, on the basis of the presented data, are apomorphine and phentolamine.

The efficacy and safety of alprostadil as monotherapy or in combination with one or more vasoactive drugs (e.g. phentolamine) has been shown by several authors.[57-63] The application of the drug is as an intracavernosal injection or as a transurethral alprostadil pellet, the medicated urethral system for erection (MUSE). The difference between alprostadil and sildenafil is in the mechanism of action. Alprostadil relaxes the smooth muscle directly and the patient can have erections in the absence of sexual arousal, and the participation of the partner is minimised.[64] In contrast, sildenafil intensifies the action of cGMP and the drug is effective only when cGMP production in penile tissue is increased by central or reflex sexual arousal, enhancing the role of the partner.[6,64] Besides this, the invasive route of alprostadil application is the main reason that is considered second-line therapy for ED (for patients not responding to first-line therapy). Because of these differences, it is not possible to make a comparison between sildenafil and alprostadil.

McMahon et al.[65] analysed 2 interesting aspects of sildenafil and intracavernosal alprostadil therapy: (i) sildenafil administration if treatment with intracorporeal injection fails; and (ii) safety of sildenafil administration in combination with triple agent intracorporeal injection therapy. Their study included 93 patients, who were nonresponders to intracorporeal injection therapy (intracavernosal alprostadil monotherapy followed by a high dose triple agent intracavernosal injection consisting of alprostadil, papaverine and phentolamine). 66% of the patients were successfully treated with sildenafil monotherapy or with sildenafil plus intracavernosal injection therapy (combination therapy). Response to prior therapy did not predict patient response to sildenafil. Furthermore, according to these findings patients who do not respond to either sildenafil or intracavernosal injection therapy (as second-line therapy) could be treated with combination therapy. Adverse effects were reported in 31% (29 of 93) of patients treated with intracavernosal injection therapy, 37% (34 of 93) of patients treated with sildenafil and in 33% (20 of 61) of patients treated with combined therapy. The incidence of dizziness was higher in men treated with combination therapy (20%; 12 of 61) than with sildenafil monotherapy (5%; 5 of 93). In all of these 12 patients, cavernosal veno-occlusive dysfunction as cavernosal venous leakage was diagnosed. The authors suggested that the increased incidence of dizziness suggests a possible potentiation of hypotensive effect of sildenafil by papaverine (a nonspecific PDE inhibitor) released from the corpora into the systemic circulation because of defective veno-occlusive mechanism. This is clinical confirmation of an interaction between sildenafil and a PDE inhibitor. Caution is therefore required if the combination therapy is used in patients with cardiovascular disease, and especially in those with cavernosal venous leakage. The profile of other adverse effects with the combination therapy was similar to each individual therapy (typical sildenafil adverse effects plus penile pain which is an adverse effect of intracavernosal injection occurred in 25% of patients) and the majority of the adverse effects were mild or moderate in severity. The treatment discontinuation rate was very low: 3 patients receiving sildenafil monotherapy and 4 patients receiving combined therapy group withdrew from the study.

4. Risks and Benefits for Different Subgroups of Patients

It is important to emphasise when evaluating the risks and benefits of sildenafil treatment that ED is a very common health problem with high prevalence and one that has considerable impact on the interpersonal relationships and quality of life of aging men.[1,2,66] According to the results of clinical trials, the benefits of sildenafil are confirmed in patients with ED of various aetiologies, as it is shown in table I. Sildenafil is prescribed in clinical practice on an as needed basis, 1-hour before sexual activity, and the half-life of the drug is about 4 hours. Considering these facts it is easy to see that any adverse effects of a sildenafil should be transient and mild in severity, associated with a very low discontinuation rate, and comparable to those

seen with placebo. Postlaunch clinical trial experience confirmed the profile of the most common adverse effects in the pre-approval period.[8,14,17,18,20,21] Therefore, based on evidence available to date, sildenafil has an acceptable risk-benefit ratio for a large proportion of men with ED, as outlined in table II.

Severe adverse effects are not acceptable for a treatment for ED. Because of the anecdotal reports of severe adverse events associated with sildenafil use, most authors in the postmarketing period have focused their activities on the analysis of the safety of use of this agent in patients with cardiovascular disease. The results of the analyses of the data regarding cardiovascular deaths and recent clinical studies have not shown a higher incidence of severe adverse effects in patients with cardiovascular disease treated with sildenafil.

The recommendations for appropriate sildenafil use in different subgroups of patients are shown in table II. The problem for the practising physician is the patient who needs assessing on an individual basis because of the lack of controlled clinical data for the particular situation. As mentioned previously, sildenafil is clearly contraindicated in patients taking nitrates. Increasing the dose of sildenafil is significantly associated with higher cGMP plasma levels. Thus, the effects of sildenafil on haemodynamic parameters have nitrate-like characteristics, but the potential to produce a marked effect, when administered alone, is minimal and transient.[23] Physicians should carefully consider whether the patients with underlying cardiovascular disease could be affected adversely by such vasodilatatory effects, especially in combination with sexual activity.[66] When evaluating this group of patients and in accordance to ACC/AHA recommendations, cardiac testing (e.g. a pre-sildenafil treadmill test) and initial monitoring of blood pressure after sildenafil usage should be performed.[30,31] This could be helpful in identifying patients at higher risk for cardiovascular events.

Headache and other nitrate-like vasodilatatory symptoms are the most common adverse effects of sildenafil, but they are generally mild and transient in nature. Sildenafil can be administered safely to patients receiving concomitant antihypertensive therapy, and no increase in adverse effects were observed in an analysis of 18 placebo-controlled studies involving 885 men taking antihypertensive medication.[18,37] An important factor for safe antihypertensive treatment is the use of drugs with a mechanism of action that does not involve the cGMP pathway.[24] Data on patients taking more than 3 antihypertensive drugs are very limited and further evaluation is necessary.

Concomitant use of sildenafil and inhibitors of cytochrome P450 (CYP) isoenzymes (e.g. cimetidine, erythromycin, ketoconazole, itraconazole, viral protease inhibitors such as ritonavir and saquinavir) is associated with increased plasma concentrations of sildenafil that could result in a higher incidence of adverse effects.[31,41,67-69] In order to minimise the risk and to prevent possible adverse effects in patients taking one of these drugs, the recommended starting dose of sildenafil should be 25mg. Similar dosage recommendations are also applicable for elderly patients and for those with hepatic disease or severe renal impairment.[41] In patients taking ritonavir, it is recommended not to exceed a maximum single dose of 25mg of sildenafil in a 48-hour period.[68]

Visual disturbances are the result of PDE6 inhibition but the risks for the patients with rare retinal genetic phosphodiesterase defect (retinitis pigmentosa) can be only presumed and difficult to confirm in practice.[25-27,41,70]

The occurrence of priapism (painful erections of long duration) is a logical concern for many physicians and investigators in clinical trials. It should be pointed out that no cases of priapism associated with sildenafil use have been reported in large clinical trials conducted in the premarketing phase.[8,9,18,19] Priapism has been reported very rarely since the drug has been marketed.[71,72] The patient should be warned to seek immediate medical assistance if priapism (an erection lasting longer than 4 hours) occurs.[14] The patients with predisposition to priapism (table II) are also presumed as high-risk for sildenafil treatment.[71]

5. Conclusion

The benefits of sildenafil treatment in a large group of patients with ED have been confirmed in clinical trials and conducted in the pre- and post-launch phases.[14,20,21] It has been proved that the drug should not be used in patients receiving nitrates in therapy. Because of the mechanism of action of the drug, it should be used with caution in certain subgroups of patients. Controlled clinical data for these subgroups of patients are lacking and so the risks and benefits must be made on an individual basis. Further data will hopefully clarify the position for some subgroups of patients.

Favourable characteristics make sildenafil the first-line therapy for ED. The first clinical data concerning the application of sildenafil in combination with intracavernosal injection therapy indicates that this approach may be effective in patients not responding to either as monotherapy, but this requires further evaluation.

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