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Comparative Trial of Treatment Satisfaction, Efficacy and Tolerability of Sildenafil versus Apomorphine in Erectile Dysfunction

An open, randomized cross-over study with flexible dosing

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Abstract
Objective: Sildenafil and apomorphine are oral agents for the improvement of erection hardness. The aim of the study was a direct comparison of the two compounds under clinical routine conditions.
Methods: 131 previously untreated men with erectile dysfunction (ED) were enrolled in a cross-over trial and randomly allocated to 50 mg sildenafil or 2 mg apomorphine. Dose-adaptation was allowed as required.
Results: Improvements in rigidity, the capacity to get and maintain an erection, and sexual confidence were statistically significantly larger with sildenafil ($p < 0.0001$). 90% of the men were satisfied with sildenafil as compared to 46% with apomorphine. At study end, 95% of the patients preferred sildenafil. Both agents were well tolerated.
Conclusions: In this cross-over comparison under clinical routine conditions men reported superior efficacy of sildenafil vs apomorphine together with a statistically significantly higher treatment satisfaction.

Key words: sildenafil, erectile dysfunction, treatment satisfaction, apomorphine.

Introduction

Erectile dysfunction (ED) affects more than 150 million men world-wide (McKinlay 2000). A survey of male sexuality in Cologne, Germany, reported an overall prevalence of 19.2% for the 30-80 year old. The prevalence showed a steep increase with age and amounted to 53.4% in men over 70 years (Braun et al. 2000). ED, however, is not only an age-dependent phenomenon. In younger men, too, there are various diseases and risk factors impairing erectile function: In a cross-section survey of members of the Israeli army 22% of men aged below 40 complained of erectile dysfunction (Heruti et al. 2004). In western societies common morbidities such as lipid disorders, diabetes mellitus, hypertension and coronary artery disease are known risk factors of ED (Kaiser et al. 1988; Lee et al. 1994; Nicolosi et al. 2003). The increasing prevalence of ED with age is primarily due to the fact that these risk factors are more common later in life (Feldman et al. 1994).

Furthermore, in many cases ED has a major impact on those affected by it as well as on their partners, and it may lead to decreased self-esteem. This not only influences sex life, but also leads to a markedly diminished quality of life of both the patients and their partners (Litwin et al. 1998; Rust et al. 1988; Tomlinson and Wright 2004; Wagner and Fugl-Meyer 2000).

There are several options in treating ED: penis prostheses, vacuum pumps, intracavernous injection of vasoactive substances, transurethral application of alprostadil and as method of choice oral medication (Howard et al. 2002) which has come to dominate ED therapy (Hanash 1997; Jarow et al. 1996).

However, there is a scarcity of data in the literature from valid direct head-to-head comparisons of oral ED therapies including their effects on ED-related psychosocial consequences and patients' satisfaction with therapy.

In 1998, oral sildenafil and in 2001, sublingual apomorphine were approved for the treatment of ED. Sildenafil acts directly on the smooth muscle cell of the cavernous bodies by selective inhibition of the enzyme phosphodiesterase 5 (PDE-5) which catalyses hydrolysis of cGMP. cGMP is the most relevant intracellular second messenger of erectile hardness which leads to the relaxation of smooth penile muscles, thus triggering erection.

Hence, the effect of endogenous nitric monoxide is enhanced by the pharmacological mechanism of PDE-5 inhibition. Nitric monoxide is released from the NANC synapses of the parasympathetic nerve endings and it induces cGMP production via activation of guanylate cyclase (Langtry and Markham 1999).

Apomorphine is a central dopamine agonist of D1 and D2 receptors with a predominance of its effects on D2 receptors. By stimulation of hypothalamic dopaminergic pathways erection-inducing stimuli are conveyed to the periphery, i.e. to the cavernous bodies (Heaton 2000).

Efficacy and safety of sildenafil and apomorphine have been demonstrated in a variety of large placebo-controlled clinical studies in a wide range of patient populations (Howard et al 2002; Jeremy and Heaton 2001).

For therapeutic decisions in daily practice evidence

from direct comparisons of efficacy and safety data of the aforementioned substances under conditions of clinical routine is of great value. The present comparative trial investigating sildenafil and apomorphine was planned based on this rationale.

Patients and Methods

In an open, randomized cross-over study, tolerability, safety and efficacy of as well as satisfaction with sildenafil and apomorphine were compared under clinical routine conditions in men with erectile dysfunction. The study was carried out in accordance with the Declaration of Helsinki (revised version of Edinburgh, 2000) and ICH-GCP guidelines. Approval was obtained from all ethics committees responsible for the individual study sites. A total of 15 sites in Germany and Austria participated. Written informed consent was obtained from all patients.

Patients

Ambulatory patients with ED who had not previously received drug therapy and were living in a stable partnership were eligible for enrolment provided they had an IIEF-5 (Sexual Health Inventory-Male) score of ≤21 (Rosen et al. 1999). Any non-drug measures to treat ED had to be stopped prior to study start.

Major exclusion criteria were hypersensitivity to any components of the study medication or to opiates, major genital deformities leading to difficulties in performing intercourse, serious cardiovascular diseases in medical history such as angina pectoris, peptic ulcers and retinitis pigmentosa. Likewise, patients were excluded if they were on therapeutics known for ED-inducing side effects such as beta blockers or with a potential for relevant interactions with sildenafil or apomorphine. Alcohol or drug abuse were also exclusion criteria as was participation in another clinical study within the last 30 days.

Study Design

The study started with a 2-week run-in-phase, followed by 2 treatment phases, each lasting for 8 weeks, separated by a 2-week wash-out period. Patients were randomized 1:1 to either of two treatment sequences (sildenafil/apomorphine or apomorphine/sildenafil). Initial doses were 50 mg of sildenafil or 2 mg of apomorphine. Dependent on efficacy and tolerability dose adjustments by the investigator were permitted after 4 weeks of treatment: sildenafil 25 – 100 mg, apomorphine 2 – 3 mg. During the second treatment phase patients were given the alternative therapy. Study medication was to be used on demand and in accordance with the approved labeling.

Throughout the study patients kept a diary on sexual activities. At the beginning of each treatment phase erectile function was determined by means the Erectile Function domain of the International Index of Erectile Function (IIEF) (Rosen et al. 1997). Treatment results were assessed at the end of each of the 8-week treatment phase with the IIEF questionnaire, the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire (Althof et al. 2003) as well as two questions as to the global judgment on efficacy. Question 1 was: Has the treatment you have been receiving during the last 4 weeks improved your erection as compared with no treatment? Question 2 was: Did the treatment you have been receiving during the last 4 weeks enable you to have a better intercourse? Patients were asked whether adverse events (AEs) had occurred, and any AEs were documented continuously.

Statistics

Based on results from previous placebo-controlled studies mean expected therapeutic results (Erectile Function Domain Score) of 21.3 for sildenafil and 18.7 for apomorphine were assumed for the sample-size estimation. To identify a statistically significant difference between the two treatments at a two-sided significance level of 0.05 with a power of 90%, 52 patients were needed per sequence. Assuming that data of 80% of the patients would be available for the cross-over analysis, 128 patients had to be enrolled.

An intention-to-treat (ITT) analysis was carried out for all endpoints. This included all patients who had taken at least one dose of study medication during either treatment phase and from whom sufficient efficacy data were available from both treatment phases to allow for at least one analysis.

Primary endpoint was EF which was a composite of questions 1-5 (scale 0-5) and question 15 (scale 1-5) of the IIEF. Therefore, the sum of scores could range from 1-30. Secondary endpoints were the individual questions of the IIEF and the EDITS questionnaire together with the domains of orgasmic function (OF), sexual desire (SD) of the IIEF and satisfaction with the treatment (EDITS – questionnaire, domains of intercourse satisfaction (IS) of the IIEF and overall satisfaction (OS)). Additionally considered were questions as to the global judgment on efficacy and the percentage of successful intercourse attempts taken from the patient diaries and the concluding question which therapeutic option the patient would prefer for the future.

EF data were assessed at the end of each treatment phase, and the treatments were compared using analysis of covariance. Covariates were EF-baseline status, age, study site as well as duration and etiology of ED.

Additionally, the cross-over model included the variables patient, phase and treatment sequence. The statistical tests were two-sided at a significance level of 0.05. Interactions by treatment phase were analyzed by incorporating treatment sequence as a variable in the ANCOVA model.

The other domains of the IIEF, individual questions of the EDITS and the data from the patient diaries were analyzed using the same model. Answers to single questions of the EDITS were given on a 0-4 scale. The mean EDITS index was calculated for each patient by multiplying the average score of the individual items of the questionnaire by 25. A patient was considered as being satisfied with the treatment if the mean EDITS index exceeded 50. This was analyzed by logistic regression. The individual questions of IIEF and EDITS were shown descriptively as categorical variables with absolute and relative frequencies. Global

judgment on efficacy was evaluated by logistic regression, the question of which therapeutic option the patient would prefer in future by Mc Nemar's test.

RESULTS

DEMOGRAPHY AND TREATMENT

A total of 131 patients were enrolled into the study, 68 of whom were randomized to sildenafil as first treatment, then apomorphine (SDN/APO-group), 63 to apomorphine as first therapy, then sildenafil (APO/SDN -group).Two patients of the APO/ SDN -group withdrew prematurely without having taken any study medication and, consequently, were not included in the analysis of safety.

Eleven patients did not complete the study according to protocol. One patient died during the study period, 1 patient dropped out due to an AE, 9 further patients terminated the study prematurely for various reasons unrelated to the study medication. For 13 patients efficacy data for the two treatment sequences were insufficient, 8 of whom completed 1 treatment phase only. After excluding these 13 patients the remainder of 116 patients were included in the ITT-analysis.

Most patients were aged 45-64 years, by far the majority being Caucasian. Demographic data of the study population are shown in Table 1. There were no relevant differences between the two treatment groups. In the SDN/APO-group ED duration since first diagnosis was 4.2 years on average (0.2 – 30.6), in the APO/SDN –group 3.5 years (0.1 – 13.8). Etiology of ED was distributed as given in Table 2. ED had gradually evolved in over 70% of the cases (79.4% SDN/APO, 75.4% APO/SDN), 63% of patients in the SDN/APO group and 62% in the APO/SDN group confirmed having nocturnal erections.

The cardiovascular risk profile was as follows: hypertension 27.9%, diabetes mellitus 9.3%, dyslipidemia 7.0% and coronary artery disease 4.6%. The vast majority of the patients (88%) had their apomorphine dose increased from 2 mg to 3 mg during the study. The sildenafil dose was increased from 50 mg to 100 mg in 55% of the patients and was reduced to 25 mg in 5%.

Table 1. Demographic Data.

	APO/SDN-group (n = 61)	SDN/APO-group (n = 68)
Age (years):		
<18	0	0
18-44	10 (16.4%)	17 (25.0%)
45-64	42 (68.9%)	39 (57.4%)
>=65	9 (14.8%)	12 (17.6%)
Mean (standard deviation)	53.5 (12.0)	52.8 (11.9)
Range	24-77	22-74
Ethnicity:		
White	59 (96.7%)	68 (100.0%)
Black	1 (1.6 %)	0
Other	1 (1.6%)	0
Weight (kg):		
Mean (standard deviation)	84.6 (11.7)	85.2 (11.7)
Range	63.0-118.0	62.0-115.0
N	61	65
Height (cm):		
Mean (standard deviation)	177.8 (7.3)	178.2 (7.5)
Range	160.0-197.0	157.0-193.0
N	61	65

APO = apomorphine; SDN = sildenafil

Table 2. Etiology of Erectile Dysfunction.

	APO/SDN-group (n = 61) n (%)	SDN/APO-group (n = 68) n (%)
Mostly psychogenic	23 (37.7)	18 (26.5)
Mostly organic	17 (27.9)	19 (27.9)
Mixed	21 (34.4)	31 (45.6)

APO = apomorphine; SDN = sildenafil

EFFICACY AND TREATMENT SATISFACTION

Erectile function (EF) improved on sildenafil by a mean of 10.5 IIEF score points (LS mean 10.2) and on apomorphine by a mean of 3.3 points (LS mean 3.1), with the improvement on apomorphine being statistically significantly smaller ($p < 0.0001$) than on sildenafil (Fig. 1).

With sildenafil 62.7% of intercourse attempts were successful, whereas this was the case in just 28.3% with apomorphine. These results were supported by the data from questions as to the global judgment on efficacy. Significantly more patients reported improved erections with sildenafil (88.7% vs. 43,1% with apomorphine, $p <0.0001$) as well as improved ability to perform intercourse (89.% vs 42.2%, $p <0.0001$). For other efficacy variables, too, sildenafil proved statistically significantly superior ($p <0.0001$) (Table 3). When looking at IIEF questions 2, 3 and 4 separately, patients on sildenafil reported statistically significantly greater improvements ($p <0.0001$) of the rigidity and the capacity to get and maintain an erection for penetration (Table 4). Accordingly, the number of patients who were confident to in getting and maintaining an erection on sildenafil increased by a factor of seven (Table 5).

Treatment satisfaction on sildenafil as assessed by EDITS was at an (LS) mean EDITS index of 74 as compared to 47 on apomorphine. Based on an EDITS index of >50 as a criterion for treatment satisfaction 90% of the patients were satisfied on sildenafil compared to 46% on apomorphine ($p <0.0001$). This statistically significant difference was confirmed by the results from the corresponding IIEF domains as satis-

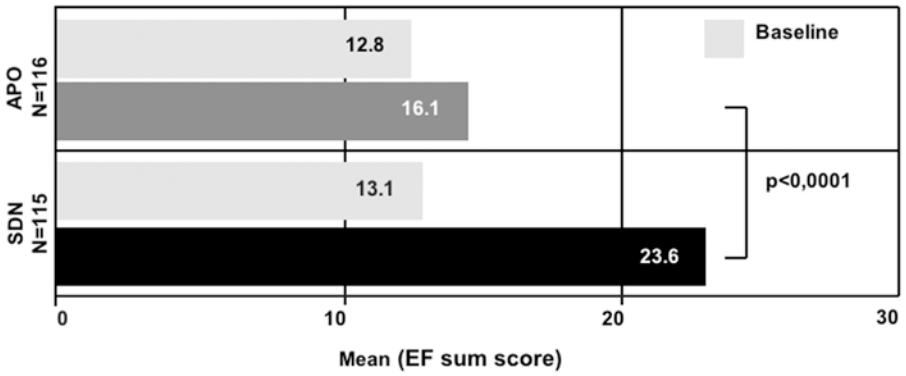

Fig. 1. Improvement of erectile function assessed by change in IIEF erectile function domain (questions 1-5 and 15, maximum score 30); ITT.

Table 3. Efficacy of Sildenafil in Comparison to Apomorphine.

IIEF Domain	Adjusted* mean value at end-of-treatment (95% CI)		Adjusted mean treatment difference (95% CI)
	SDN	APO	
Erectile function	23.1 (21.8; 24.4)	15.7 (14.5; 17.0)	7.2 (5.5; 8.8) # &
Orgasmic function	8.6 (8.1; 9.1)	6.7 (6.2; 7.2)	1.9 (1.2; 2.5) &
Sexual desire	7.6 (7.3; 7.9)	6.8 (6.5; 7.1)	0.8 (0.4; 1.2) &

APO = apomorphine; SDN = sildenafil
* Least square mean (LS mean)
# Difference of therapeutic effect (improvement of EF under therapy) between the two groups. Therapeutic effect SDN 10.2; APO 3.1
& p<0.0001

Table 4. Improvement of Sexual Function according to Answers to Questions 2, 3 and 4 of the IIEF.

	IIEF – question 2 Mean score (SD*)		IIEF – question 3 Mean score (SD*)		IIEF – question 4 Mean score (SD*)	
	SDN	APO	SDN	APO	SDN	APO
n	115	116	114	116	115	116
Before therapy	2.1 (1.2)	2.1 (1.3)	2.3 (1.4)	2.1 (1.4)	2.0 (1.3)	1.9 (1.3)
On therapy	4.1 (1.4)	2.7 (1.5)	4.0 (1.3)	2.8 (1.5)	3.8 (1.4)	2.5 (1.4)
Difference	1.9 (1.5)	0.6 (1.3)	1.8 (1.5)	0.7 (1.2)	1.8 (1.6)	0.6 (1.2)

APO=apomorphine; SDN=sildenafil
*Standard deviation

Table 5. Changes in the Confidence in getting and maintaining an Erection on Therapy.

Degree of confidence	Before therapy		After therapy	
n (%)	Sildenafil 114 (100%)	Apomorphine 116 (100%)	Sildenafil 115 (100%)	Apomorphine 116 (100%)
Very high	0 (0%)	1 (1%)	22 (19%)	3 (3%)
High	10 (9%)	12 (10%)	52 (45%)	23 (20%)
Moderate	31 (27%)	26 (22%)	26 (23%)	34 (29%)
Low	37 (33%)	37 (32%)	10 (9%)	30 (26%)
Very low	36 (32%)	40 (35%)	5 (4%)	26 (22%)

faction with sexual intercourse and global satisfaction (Fig. 2.).

In addition to the overall EDIT-data assessment an analysis of the individual items was carried out. Sildenafil was statistically significantly superior to apomorphine for each item. More specifically, 76% of the patients on sildenafil were very satisfied or satisfied with the time to onset of action (apomorphine 31%), 72%

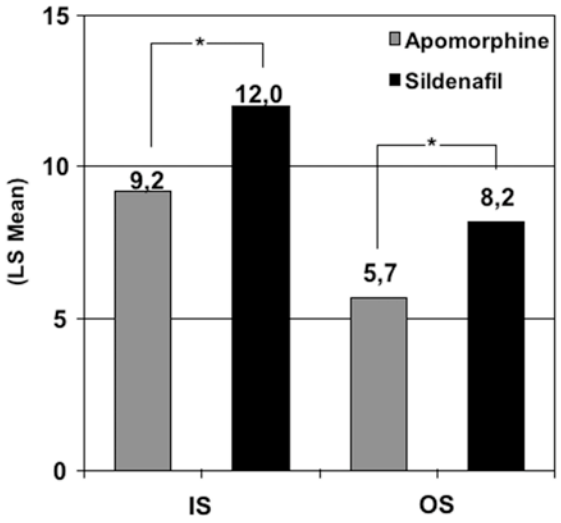

Fig. 2. Satisfaction with sildenafil und apomorphine assessed by IIEF domains intercourse satisfaction (IS) and overall satisfaction (OS). * p < 0,0001 (IS: IIEF questions 6 – 8, maximum score 15; OS: questions 13 und 14, maximum score 10); ITT.

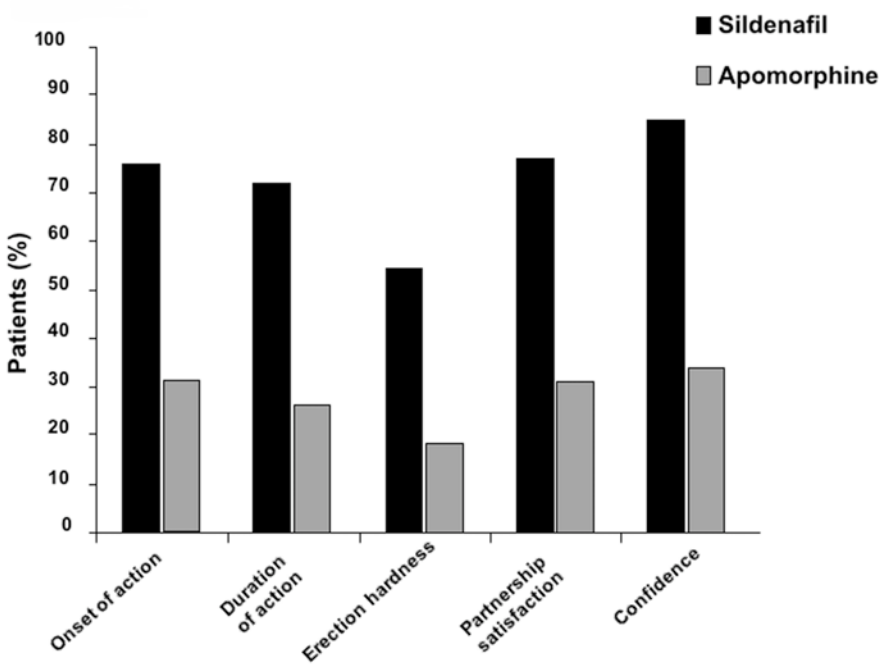

Fig. 3. Satisfaction with efficacy, partnership and confidence (EDITS Items 5,6,11,9,7,1; % of patients: satisfied or very satisfied, harder or much harder, more confident or much more confident); ITT.

Table 6. Adverse Events (AEs).

	Sildenafil n (%)	Apomorphine n (%)
Number of AEs	65	35
Patients with AEs	45 (35.7)	27 (21.8)
Patients with serious AEs*	2 (1.6)	1 (0.8)
Withdrawals due to AEs	0	1 (0.8)
Dose reductions due to AEs	8 (6.3)	5 (4.0)

*Two patients with serious AEs (sudden cardiac death; perforated appendicitis) are not listed, because the events occurred more than 7 days after the last intake of study medication.

with the duration of action (apomorphine 26%) and 54% felt that the erection was much harder or harder than without therapy (apomorphine 18%). Partner satisfaction was 77% (apomorphine 31%). Sexual self-confidence rose accordingly with sildenafil treatment; 85% of the patients (apomorphine 34%) were confident in being able to enter into sexual activities (Fig. 3). After study end 95% of the patients (p <0.0001) were in favor of treatment with sildenafil.

Safety and Tolerability

All in all, 65 adverse events (AEs) were reported from 45 patients on sildenafil and 35 AEs from 27 patients on apomorphine (Table 6). The safety profile was compatible with that known from other clinical studies. Most frequent AEs on sildenafil were headache (10.3%), flush (7.1%), dyspepsia (5.6%) and rhinitis (4.8%), most common on apomorphine were headache (3.2%) and nausea (5.6%). One patient withdrew from therapy with apomorphine due to a non-serious AE (abdominal pain). Five serious AEs were reported in 5 patients: stricture of the urethra on apomorphine, exacerbation of chronic bursitis and stroke

on sildenafil as well as a case of perforated appendicitis during the follow-up phase. One patient died of sudden cardiac death during the apomorphine treatment phase. For the week preceding the event no documentation on the intake of study medication was available. None of the serious AEs were considered by the investigators as being causally related with the study medication.

Discussion

It is now generally accepted that ED is one of the most frequent, if not the most common civilization disease. In Germany up to 20% of men aged 30-80 years were shown to be affected (Braun et al. 2000). The fact that ED almost always has an impact on 2 persons living in a partnership, leading to a de facto doubling of the number of persons affected, illustrates its medical and social relevance.

Various international studies convincingly demonstrated the psychological and social consequences for the patient himself, his partner and the social environment of both including marked negative effects on self-esteem and quality of life.

Evidence from several clinical studies has shown that recovery of erectile function and satisfactory sex life can restore self-esteem and quality of life of the patients (Althof 2002; Althof et al. 2003; Gil et al. 2001; Paige et al. 2001; Tomlinson and Wright 2004).

Even before the era of highly efficient oral pharmacotherapy with sildenafil most ED patients preferred oral therapy although it was inferior to the more invasive methods (Hanash 1997; Jarow et a. 1996). Decisive factors for the acceptance of therapeutic methods apart from efficacy are safety and tolerability as well as the potential to restore an undisturbed sex life in the most natural of ways (Hanson-Divers et al. 1998).

In the present direct comparison between two oral ED medications the assessment of efficacy and tolerability was one of the major criteria to investigate to what extent the two medications would be able to ensure global satisfaction with sex life which in turn was understood to be paramount in the preference for either of the medications.

As shown by the results of the study sildenafil, when compared directly to apomorphine, was statistically significantly superior for all domains of the IIEF investigated as well as for the EDITS global score. This was clearly reflected by the 90% vs 46% rates of treatment satisfaction and the 95% vs 5% preference rates in favor of sildenafil.

In the meantime results of three direct comparisons of apomorphine SL and sildenafil have been published, all of which confirmed that sildenafil was statistically significantly superior to apomorphine (Eardley et al. 2004; Perimenis et al. 2004 a; Perimenis et al. 2004 b).The comparative study investigating sildenafil and apomorphine by Ian Eardley and co-workers was very similar to the present one and resulted in a markedly greater therapeutic satisfaction for patients on sildenafil (mean EDITS Index of 83 for sildenafil vs. 47 for apomorphine). Of 117 patients 113 preferred sildenafil, only 4 patients preferred apomorphine (Eardley et al. 2004).

Clearly, there are limitations in the present study as well as in the other comparative trials mentioned above in that they were all carried out in an open design. A double-blind design, however, would hardly have been practicable due to the differences in application and pharmacokinetics of the two medications. Besides, a double-blind design would not have been adequate to reflect real life conditions. Therefore, the open study design was deliberately chosen. No disadvantage as a result of this was noted for either of the medications.

Finally, the IIEF scores obtained for sildenafil in this study, the success rates (patient diaries) and the rates of satisfaction as assessed by EDITS were all in good agreement with the results of many published double-blind or open uncontrolled studies with sildenafil (Cappelleri et al. 2004; Carson et al. 2002; DeBusk et al. 2004; Dinsmore et al. 1999; Duttagupta et al. 2001; Gil et al. 2001; Gilholly et al. 1999; Goldstein et al. 1998; Lewis et al. 2001; Mancia et al. 2002 ; Raina et al. 2003).

Conclusions for Clinical Practice

Whereas a high level of tolerability was reported for both medications in a direct open comparison, the efficacy of sildenafil was statistically significantly superior to that of apomorphine (EF, therapeutic effects 10.5 for sildenafil vs. 3.3 for apomorphine). The same was true for global satisfaction (90% for sildenafil vs. 46% for apomorphine). This has translated into an overwhelming preference of sildenafil (95%) by the patients.

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