

A 4-YEAR UPDATE ON THE SAFETY OF SILDENAFIL CITRATE (VIAGRA[®])

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ABSTRACT

Clinical studies have demonstrated that sildenafil citrate (Viagra) is an effective and well-tolerated oral treatment for erectile dysfunction. Despite its established safety profile, concern about its cardiovascular safety persists among some physicians and the general public. This concern has stemmed primarily from sporadic reports of adverse events published in the literature and sensationalized by the media. However, the only absolute contraindication for sildenafil is concurrent use of nitrates. Because sildenafil has been on the market for 4 years and under clinical investigation for even longer, we can now evaluate its long-term safety in men who have been taking the drug for several years. We review this issue from 3 perspectives. First, we reassess the overall safety profile of sildenafil by reviewing the initial controlled clinical trials and open-label studies. We present new data from patients who have been exposed to sildenafil for up to 4.5 years. We also evaluate the results from independent postmarketing studies. Second, we review the cardiovascular-specific results from the clinical trials, long-term extension, and postmarketing studies. Lastly, we review the specific effects on the visual system based on findings from studies conducted during drug development and post marketing. *UROLOGY* **60** (Suppl 2B): 67–90, 2002. © 2002, Elsevier Science Inc.

Since the approval of sildenafil citrate (Viagra; Pfizer Inc, New York, NY) for the treatment of erectile dysfunction (ED) by the US Food and Drug Administration (FDA) in 1998, numerous clinical studies have demonstrated that sildenafil is effective and well tolerated in patients with ED of broad-spectrum etiology. Despite its demonstrated effectiveness and established safety profile, concern persists among some physicians and the general public about the cardiovascular safety of sildenafil. The heightened concern has stemmed primarily from sporadic case reports of adverse

events (AEs) that have been published in the medical literature and sensationalized by the media. In 1998, the FDA published a report on 130 confirmed deaths among men (mean age, 64 years) who had received prescriptions for sildenafil during the first 8 months of its availability (late March to mid-November 1998), a period during which >6 million prescriptions for sildenafil had been filled.¹

Concerns about the cardiovascular safety of sildenafil developed despite the fact that the cause of death was not mentioned or was unknown for 37% of the cases, dosing information was not reported for 52% of cases, and the time from sildenafil ingestion to death or onset of symptoms was not available for 48% of patients. Given that a large proportion of the essential information was either unmentioned or missing in these reports, it is impossible to draw firm conclusions about the causal relation between sildenafil use and these deaths simply because of their temporal relation with dosing. In a more recent analysis of AEs reported to the FDA between March 1998 and August 1999, important information was again missing from these reports: medical histories, cause of death, and sil-

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denafil dosing were not available for 35%, 44%, and 60% of reported deaths, respectively.²

The number of reports provided to the FDA's spontaneous AEs reporting system (MedWatch) and the quality of information reported depend on a number of factors, including the length of time a drug has been on the market and available by prescription, the amount of the market share it has gained, the amount of publicity it has received, and whether the event is reported by a healthcare professional or a lay person.³ As such, the FDA advises that "it is not possible to calculate a true incidence rate of a particular event for a specified drug"¹ based on data from the spontaneous AE reporting system because neither the true numerator nor the true denominator are known. In its reports, the FDA also notes that conclusions on causality cannot be drawn from these data, and they caution against using the data from this system to compare AE rates among different treatments.

Sildenafil has been on the market for 4 years and under clinical investigation for even longer. Thus, it is now possible to systematically evaluate the long-term safety of sildenafil in men who have been taking the drug for several years. In this review, we examine the safety profile of sildenafil from 3 perspectives. First, we reassess the overall safety of sildenafil by reviewing the results from the 18 double-blind, placebo-controlled trials and 10 open-label phase II/III studies that were included in the New Drug Application to the FDA for sildenafil, as first described by Morales *et al.*⁴ More recently, Steers *et al.*⁵ reported the open-label results from a subset of these patients. For the first time, we present new data from a subset of patients that began 4 additional years of open-label sildenafil treatment at the end of previous double-blind parent trials and initial open-label studies. As of this writing, data were available for patients completing the third year of open-label treatment such that in total, these patients have been exposed to sildenafil for up to 4.5 years. This is the longest duration of sildenafil treatment to be examined systematically for tolerability in a clinical population. We also present relevant results from 2 additional subanalyses performed on data pooled from 25 and 35 phase II/III/IV trials that had been completed at the time of post hoc analyses and which included all evaluable patients.

Although data from double-blind placebo-controlled trials provide the most accurate assessment of causality, the actual experience with sildenafil in clinical practice may differ. Therefore, we also evaluate the overall safety of sildenafil by reviewing the results of independent (ie, non-Pfizer-sponsored) postmarketing studies conducted in the clinical practice setting. All 13 of the postmarketing studies we identified were case series with pop-

ulations ranging in size from 28 to 2816 patients and treatment durations from 1 to 12 months. We summarize the overall incidence of AEs, the most common AEs, and discontinuations because of AEs.

Second, we review the safety of sildenafil as it relates specifically to potential effects on the cardiovascular system. In early clinical trials, patients randomized to receive sildenafil or placebo reported having many of the conditions commonly comorbid with ED, including hypertension, hyperlipidemia, ischemic heart disease, other cardiovascular diseases, diabetes, and depression.⁴ In these studies, patients were excluded if they had had a myocardial infarction (MI) or stroke within 6 months of enrollment, unstable angina or congestive heart failure, hypertension (>170/110 mm Hg) or hypotension (<90/50 mm Hg), uncontrolled diabetes, significant renal or hepatic disease, or if they were taking a nitrate or nitric oxide donor. We review the cardiovascular-specific results from the double-blind parent trials, initial open-label studies, and long-term (3-year) extension.

When the American College of Cardiology (ACC) and the American Heart Association (AHA) published its *Expert Consensus Document on the Use of Sildenafil in Patients With Cardiovascular Disease*,⁶ the groups were concerned that although sildenafil was generally well tolerated in most patients with cardiovascular risk factors and diseases, they concluded—based on data available at that time—that the drug was "potentially hazardous" in patients "with active coronary ischemia; those with congestive heart failure and borderline low blood volume and low blood pressure status; those with complicated multidrug antihypertensive therapy regimens; and those taking medications that may affect the metabolic clearance of Viagra." At that time, relatively few patients in these subgroups had been included in clinical trials. Since its publication, a number of clinical studies have been conducted in some of these patient populations. We identified 14 studies that included patients with cardiovascular disease,⁷⁻⁹ active coronary ischemia,¹⁰⁻¹³ and multidrug antihypertensive regimens.¹⁴⁻¹⁷

We also provide the most recent update of Pfizer's clinical safety database that contains information on the extent of exposure to sildenafil in clinical trials before and after the FDA approved the drug for marketing. As of September 30, 2001, the database contained data from 124 completed and ongoing clinical trials that involved 5054 placebo-treated and 6896 sildenafil-treated patients from the double-blind treatment studies. This represented 2593 person-years of observation. In addition, data from open-label studies represented

nearly 11,000 person-years of sildenafil exposure.¹⁸

Third, we review the safety of sildenafil as it relates specifically to potential effects on the visual system. In addition to its strong inhibitory effects on phosphodiesterase type 5 (PDE5),¹⁹ sildenafil is also a weak inhibitor of PDE6, which is found only in high concentrations in the photoreceptor cells of the retina.²⁰ Because inhibition of PDE5 and PDE6 increases intracellular levels of cyclic guanosine monophosphate (cGMP), and because cGMP is involved in phototransduction, higher plasma concentrations of sildenafil can potentially affect visual function. Thus, the visual effects of sildenafil treatment have been evaluated extensively during all stages of drug development and during the postmarketing period. We identified 17 clinical studies that examined these effects in particular or as part of their overall safety assessments.

OVERALL SAFETY OF SILDENAFIL

DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS

Morales *et al.*⁴ were the first to extensively evaluate the tolerability of sildenafil in phase II/III clinical trials. In these 18 double-blind, placebo-controlled trials, patients were randomized to receive sildenafil (n = 2722) or placebo (n = 1552) treatment for up to 6 months. Of the 11 trials in which study drug was taken on an as-needed (PRN) basis, 5 used a fixed-dosing schedule to provide insight on the safety of sildenafil by dose. Six trials used a flexible-dosing regimen, whereby the starting dose of study drug (50 mg) could be adjusted to 25 mg or 100 mg based on efficacy and tolerability. Flexible-dosing schedules most closely resemble the dosing patterns used in clinical practice.

In the fixed-dose trials, the overall incidence of treatment-related AEs increased as the dose of sildenafil increased. Likewise, the occurrence of the most commonly reported treatment-related AEs (ie, headache, facial flushing, dyspepsia, rhinitis [nasal congestion], and abnormal vision) was also dose related, ranging from 0.3% (abnormal vision) to 10% (headache) at 25 mg, 0.4% (abnormal vision) to 19% (flushing) at 50 mg, and 4% (rhinitis) to 22% (headache) at 100 mg of sildenafil. AE incidence rates among placebo-treated patients ranged from 0.2% (rhinitis) to 4% (headache).²¹ Discontinuations because of treatment-related AEs were comparable at the 25-mg (0.6%) and 50-mg (0.4%) doses of sildenafil; the rate increased slightly with the 100-mg dose (1.2%). The discontinuation rate in the placebo group was 1.0%. The most common AE resulting in discontinuation was headache, which accounted for 0.6% in the 100-mg sildenafil group.⁴

In the flexible-dose trials, the incidence rates of

the most commonly reported AEs (from all causes) were higher in sildenafil-treated versus placebo-treated patients; however, discontinuation rates because of all-causality AEs were similar in the 2 treatment groups (2.5% and 2.3%, respectively). Headache (1.1%), facial flushing (0.4%), and nausea (0.4%) were the most common AEs leading to discontinuation in the sildenafil group, and headache (0.4%) was the most common AE leading to discontinuation in the placebo group.

Overall, the results obtained from pooling data from 18 double-blind placebo-controlled trials demonstrate that sildenafil is a well-tolerated oral therapy for ED. In both the fixed-dose and flexible-dose PRN studies, the AEs reported were mostly transient and mild to moderate in severity, and the rate of discontinuations because of AEs was low and comparable between patients who received sildenafil and those who received placebo.

In a retrospective analysis of data pooled from 25 double-blind, placebo-controlled trials (which included the 18 phase II/III trials), Osterloh *et al.*²² examined the overall efficacy and safety of sildenafil in nearly 6000 patients, and in more detail of patients who were stratified by existing comorbid conditions, such as diabetes, hypertension, and ischemic heart disease.²² The most commonly reported AEs for all patients and for specific comorbidities included headache, facial flushing, dyspepsia, abnormal vision, dizziness, and rhinitis. The incidence rates for these events are summarized in Table I²³ by cause and comorbid condition. Although these data suggest that patients may tolerate sildenafil differently based on existing comorbidities, the discontinuation rates associated with AEs were low across the 3 subgroups: 1.9% for patients with diabetes, 2.3% in those with hypertension, and 3.6% in patients with ischemic heart disease.²³ The overall discontinuation rate associated with AEs was 2% in both the sildenafil and placebo treatment groups (Table I).

After completion of an additional 10 studies, we recently conducted a similar retrospective analysis of data pooled from 35 Pfizer-sponsored trials involving 4819 patients who received sildenafil and 3296 patients who received placebo in double-blinded fashion.²⁴ Overall, the most frequently reported AEs and their incidence rates were comparable with those in both the 18- and 25-trial analyses (Table II).²⁴ When data from the 35 trials were pooled, patients were stratified based on whether they were or were not taking antihypertensive medications. If patients were taking these drugs, further stratification was based on the number of different classes of antihypertensives they were taking (ie, 1, 2, or ≥ 3). Among sildenafil-

TABLE I. Most frequently reported adverse events by cause and comorbid condition (Percentages)*

	Diabetes (n = 1328)		Hypertension (n = 1582)		IHD (n = 582)		All Patients [†] (n = 5918)	
	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
All causality								
Headache	4.6	11.6	3.7	16.8	3.6	21.0	5.6	19.0
Facial flushing	1.7	7.9	3.4	13.1	0.9	13.5	2.0	14.2
Dyspepsia	1.0	7.9	1.2	9.2	1.4	10.5	1.6	8.7
Dizziness	1.7	1.7	2.1	3.7	0.9	2.2	1.9	3.1
Rhinitis	1.0	1.7	0.9	5.3	0.9	5.5	1.5	5.1
Abnormal vision	0.7	4.4	1.1	5.8	2.3	6.6	0.7	5.9
Treatment related								
Headache	2.4	7.7	2.1	12.1	2.7	16.9	3.3	14.6
Facial flushing	1.5	7.8	3.2	12.8	0.5	13.5	1.9	14.1
Dyspepsia	0.3	5.1	0.5	5.4	0.5	8.3	0.7	6.2
Dizziness	0.7	1.2	1.5	2.5	0.0	1.4	1.1	2.2
Rhinitis	0.3	1.5	0.3	2.8	0.0	1.7	0.2	2.6
Abnormal vision	0.2	3.1	0.3	5.1	1.4	5.2	0.3	5.2
Discontinuations because of adverse events	1.9	1.9	2.3	2.3	1.9	3.6	2.3	2.0

IHD = ischemic heart disease.

* Data pooled from 25 double-blind, placebo-controlled phase II/III trials. (Adapted from data on file.²³)

[†] Percentages may be higher because the "All Patients" category includes patients with diabetes, hypertension, and IHD as well as others without these comorbid conditions.

TABLE II. Most frequently reported adverse events by cause and antihypertensive therapy status (Percentages)*

	Antihypertensive Regimen								All Patients [†]	
	None		1 Class		2 Classes		3+ Classes			
	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil	Placebo	Sildenafil
All causality										
Headache	5.6	16.9	3.4	17.9	2.8	12.3	3.5	14.8	4.9	16.7
Facial flushing	1.5	13.3	1.9	14.0	2.1	11.7	3.5	8.1	1.7	13.2
Dyspepsia	1.4	6.8	1.3	7.9	0.7	8.5	0.0	5.2	1.3	7.1
Dizziness	1.6	3.3	3.1	3.2	0.7	4.3	1.7	1.5	1.8	3.3
Rhinitis	1.6	4.2	0.6	5.3	1.0	3.2	0.0	3.7	1.3	4.3
Abnormal vision	0.5	4.8	0.8	4.7	1.0	5.6	1.7	5.9	0.6	4.9
Treatment related										
Headache	3.2	13.8	1.9	13.7	2.1	9.1	3.5	13.3	2.9	13.4
Facial flushing	1.4	13.2	1.9	13.7	2.1	11.7	2.6	8.1	1.6	13.1
Dyspepsia	0.7	5.0	0.2	5.6	0.3	4.5	0.0	2.2	0.5	5.0
Dizziness	1.1	2.8	1.6	2.6	0.7	2.1	0.9	0.0	1.1	2.6
Rhinitis	0.2	2.4	0.3	2.7	0.0	1.9	0.0	1.5	0.2	2.4
Abnormal vision	0.4	4.5	0.3	3.9	0.3	5.1	0.9	3.7	0.4	4.4

* Data pooled from 35 phase II/III/IV trials. (Adapted from data on file.²⁴)

[†] Sildenafil n = 4819; placebo n = 3296.

treated patients, the incidences of AEs from all causes and of those considered treatment related were comparable between patients who were not taking any concomitant antihypertensives and those who were, even among patients taking ≥ 3 different agents. These results suggest that sildenafil is well tolerated among patients taking antihypertensive medications, including those on multi-drug regimens.

OPEN-LABEL EXTENSION STUDIES

Patients who were compliant during the double-blind treatment period of the parent study in which they participated were eligible to continue with open-label sildenafil treatment for up to 2 years. Morales *et al.*⁴ reported on the tolerability of sildenafil in 10 open-label studies (n = 2199); Steers *et al.*⁵ described the safety results from 4 of these open-label trials (n = 1008). In Morales *et al.*,⁴ the

most frequently reported AEs included headache (10%), facial flushing (9%), dyspepsia (6%), and respiratory tract infection (6%), and were generally mild or moderate. Two percent of patients discontinued because of all-causality AEs over a 1-year period, with headache being the most common reason for discontinuation. In the subanalysis by Steers *et al.*,⁵ 7% of patients reduced their dose of sildenafil or temporarily discontinued treatment because of AEs, about half of which were considered treatment related. Serious AEs occurred in 7% of patients. The most frequently occurring serious AEs were surgery, cancer, and viral chest infection. During the study, 2 patients died: 1 patient died of an acute MI (he had had a previous MI), and 1 died of a malignant melanoma. Neither the serious AEs nor the deaths were considered related to treatment by the investigators.⁵

A separate, uniquely designed study also examined the safety of extended sildenafil treatment in 401 patients with ED. The study consisted of 4 phases: (1) a 2-week, single-blind, placebo run-in phase; (2) a 16-week, open-label, flexible-dose escalation phase; (3) an 8-week, double-blind treatment phase, which included a follow-up visit 2 weeks after the end of treatment, at which time patients were randomized to placebo or sildenafil; and (4) an optional open-label phase (≤ 1 year) that started ≥ 4 weeks after the end of the double-blind phase.²⁵ The maximum exposure to sildenafil was 18 months. The most frequently reported AEs (ie, headache, dyspepsia, facial flushing) were relatively consistent during the different treatment phases. After the 1-year extension phase, the most common AEs from all causes were dyspepsia (14%), facial flushing (13%), and headache (10%). At the end of 1 year, 2 (1.2%) patients discontinued because of treatment-related AEs: 1 reported drowsiness and headache and the other reported nasal congestion and pain. There were 24 serious AEs and 1 death during the 18 months of study; none were considered related to sildenafil treatment by the investigators.²⁵

LONG-TERM OPEN-LABEL STUDIES

A subset of the patients who completed the double-blind, placebo-controlled trials and initial open-label studies was given the opportunity to continue open-label sildenafil treatment for 4 more years. As of this writing, data were available for patients completing the third year of this study. Thus, our results obtained at the end of 3 years represent the cumulative experience of patients who had been taking sildenafil for up to 4.5 years. Unlike the previous parent trials and open-label extension studies, the primary objective of this study was to assess the combined occurrence of serious AEs and observed or volunteered AEs that

resulted in a change in sildenafil dosing or a temporary or permanent discontinuation.

Of the 1410 patients who entered the initial open-label studies, 979 patients enrolled in the 4-year extension. Of this number, 955 (97.6%) were evaluable for safety at the end of the third year. The occurrence of AEs led patients to reduce their dose of sildenafil (2.4%), temporarily discontinue treatment (6.8%), or permanently withdraw from the study (5.0%). Most AEs were not treatment related, and included coronary artery disease (2.0%), prostate disorder (1.3%), carcinoma (0.9%), and MI (0.8%) (Table III). Less than 4% of patients experienced AEs that were considered related to treatment by the study investigators. The most commonly reported treatment-related AEs were headache (0.9%), dyspepsia (0.9%), and facial flushing (0.4%). Serious AEs were reported by 119 patients (12.5%); none were considered by either the investigators or the sponsor to be related to treatment. The most frequently reported serious AEs were cardiovascular in nature (see next section).

By the end of the 3-year treatment period, 314 (32.1%) patients had discontinued from the study (Table IV). Nearly half (14.6%) of the discontinuations occurred during the first 12 months of study. Discontinuation rates during the second (9.2%) and third (8.6%) years were considerably lower. Most (79%) discontinuations were not related to treatment. During the entire 3-year period, only 10 patients (1.0%) discontinued because of treatment-related AEs: dyspepsia (4), headache (2), dizziness (1), flushing (1), rhinitis (1), and leg cramping (1). Interestingly, 17 patients were withdrawn from the study because they received a prescription for, or were taking, nitrates. Because sildenafil potentiates the hypotensive effects of nitrates and nitric oxide donor drugs, use of these drugs on a regular and/or intermittent basis is an absolute contraindication and a criterion for study exclusion.

There were 6 deaths during the course of the study: MI (3), carcinoma (1), worsening of diabetes (1), and traumatic brain injury (1). All 6 patients were taking the 100-mg dose of sildenafil, but no death was considered treatment related by either the investigators or the sponsor. From entry into the double-blind, placebo-controlled parent study to the end of the 3 years of open-label treatment, total exposure to sildenafil in this cohort of patients was 3253 person-years. Thus, the corresponding all-cause mortality rate was 0.18/100 person-years and was comparable with those reported elsewhere (see next section).

TABLE III. Most commonly reported adverse events after 3 years of open-label sildenafil treatment

Adverse Event*	Treatment Related n (%)	Not Treatment Related n (%)	Total n (%)
Coronary artery disease	0 (0.0)	19 (2.0)	19 (2.0)
Prostate disorder	0 (0.0)	12 (1.3)	12 (1.3)
Dyspepsia	9 (0.9)	2 (0.2)	11 (1.2)
Carcinoma	0 (0.0)	9 (0.9)	9 (0.9)
Headache	9 (0.9)	0 (0.0)	9 (0.9)
Myocardial infarction	0 (0.0)	8 (0.8)	8 (0.8)
Abnormal vision	4 (0.4)	0 (0.0)	4 (0.4)
Facial flushing	4 (0.4)	0 (0.0)	4 (0.4)
Rhinitis	3 (0.3)	0 (0.0)	3 (0.3)
Congestive heart failure	0 (0.0)	2 (0.2)	2 (0.2)

* Serious adverse events and observed or volunteered adverse events that resulted in a change in sildenafil dose or a temporary/permanent discontinuation. Incidence rate was calculated using the total number of patients assessed for safety (n = 955).

TABLE IV. Discontinuations by year during 3 years of open-label sildenafil treatment

	Number of Discontinuations (%)*			
	Year 1	Year 2	Year 3	Total
Treatment related				
Insufficient response	23 (2.4)	17 (1.7)	16 (1.6)	56 (5.7)
Adverse event	5 (0.5)	3 (0.3)	2 (0.2)	10 (1.0)
Total	28 (2.9)	20 (2.0)	18 (1.8)	66 (6.7)
Not treatment related				
Adverse event	30 (3.1)	14 (1.4)	13 (1.3)	57 (5.8)
Lost to follow-up	21 (2.1)	17 (1.7)	18 (1.8)	56 (5.7)
Study violation	14 (1.4)	9 (0.9)	5 (0.5)	28 (2.9)
Withdrawn consent	17 (1.7)	16 (1.6)	16 (1.6)	49 (5.0)
Death	1 (0.1)	3 (0.3)	2 (0.2)	6 (0.6)
Other	29 (3.0)	11 (1.1)	12 (1.2)	52 (5.3)
Total	112 (11.5)	70 (7.2)	66 (6.7)	248 (25.3)
Grand total	140 (14.3)	90 (9.2)	84 (8.6)	314 (32.1)

* Percentages were calculated using the total number of patients enrolled (n = 979).

POSTMARKETING CASE SERIES

Since its approval for marketing, few new AEs associated with sildenafil use have been identified. Infrequent occurrences of prolonged erections (>4 hours) or priapism (>6 hours) have been reported, but most of these cases were associated with coadministration of other agents known to cause priapism (eg, intracavernosal prostaglandin therapy). Nevertheless, postmarketing studies and spontaneous reports are important sources of information for identifying new AEs that were not observed in controlled clinical trials.

By conducting an electronic search of the biomedical literature published since 1995, we identified 13 independent (ie, non-Pfizer-sponsored) studies that examined the tolerability of sildenafil in the clinical practice setting (Table V).²⁶⁻³⁸ All studies were prospective, open-label case series,

ranging in duration from approximately 1 to 12 months. Study population size was also diverse, ranging from 28 to 2816 patients. None of the studies included a placebo control group. Up to 91% of patients had used other forms of therapy for their ED, including sildenafil, before entering the studies. In general, the incidence rates of reported AEs were higher—ranging from 16% to 63%—than were those reported in controlled clinical trials. However, the most commonly reported AEs were similar to those reported in clinical trials, including headache (7% to 39%) and flushing (7% to 34%). These higher rates may be explained, at least in part, by the unrestricted nature of the study setting. For example, in 3 of the studies that report on sildenafil dosing, up to 25% of patients exceeded the approved dosing range (25 to 100 mg) by taking 150 mg and sometimes 200 mg of sildenafil.

TABLE V. Overall safety of sildenafil in postmarketing case series

Study	Duration	n*	Incidence of AEs	Most Common AEs	Discontinued because of AEs	Comments
Zippe <i>et al.</i> ²⁶	NR (≥ 4 doses)	28	NR	Headache = 39% Color vision = 11%	0%	Overall incidence of AEs could not be determined from text.
Jarow <i>et al.</i> ²⁷	6 weeks	267	35%	Headache = 15% Flushing = 14%	0%	Study conducted during initial 6 weeks after sildenafil approved for marketing by the FDA.
Lowentritt <i>et al.</i> ²⁸	NR	84	63%	Flushing = 33% Headache = 27%	1%	One discontinuation due to AE; 25% of patients exceeded 100 mg of sildenafil.
Marks <i>et al.</i> ²⁹	4–6 weeks	74	22%	Headache = 7% Flushing = 7%	3%	65% had used other forms of therapy; AEs were mild, transitory, and did not interfere with treatment.
Virag ³⁰	8 weeks	157	27%	Flushing/dizziness = 9% Headache = 8%	2%	54% of patients had been using intracavernous injection therapy successfully; strict criteria for sildenafil contraindications.
McMahon <i>et al.</i> ³¹	4.5 months [†]	278	54%	Flushing = 34% Headache = 23%	9%	91% of patients had used sildenafil previously; majority of AEs were mild; 1% used 150 mg of sildenafil.
Moreira <i>et al.</i> ³²	NR	256	32%	Flushing = 31% Headache = 25%	0%	Incidence of AEs likely overestimated because of direct patient questioning; AEs were dose related; 16 patients increased dose of sildenafil to 150 mg.
Basar <i>et al.</i> ³³	6 months	141	16%	Headache = 9% Palpitations/sweating = 4%	10%	Incidence of AEs derived from text; the mutual exclusivity of patient numbers may not be accurate.
Fagelman <i>et al.</i> ³⁴	12 months	80	48%	Headache = 16% Flushing = 13%	3%	AEs were mild to moderate and transient.
Gil <i>et al.</i> ³⁵	≥ 10 weeks	2816	20%	Headache = 10% Flushing = 9%	6%	AEs included nasal congestion (3.0%), dyspepsia (1.9%), and visual disorders (1.4%).
Guay <i>et al.</i> ³⁶	6–8 weeks	521	NR	Flushing = 20% Headache = 17%	<2%	Overall incidence of AEs could not be determined from text; treatment-related AEs were generally mild to moderate in severity.
Martinez-Jabaloyas <i>et al.</i> ³⁷	≥ 2 months	213	24%	Headache = 9% Flushing = 9%	3%	No SAEs and no cardiovascular events were reported.
Palumbo <i>et al.</i> ³⁸	6 weeks	380	22%	Headache = 15% Flushing = 8%	1%	41% of patients had used other forms of therapy; all AEs were mild to moderate in severity; no cardiovascular events were reported.

AE = adverse event; FDA = Food and Drug Administration; NR = not reported; SAE = serious adverse event.

* Number of evaluable patients, n = 5295.

[†] Mean follow-up time.

TABLE VI. Clinical trial update of incidence rates: myocardial infarction and all-cause mortality as of September 30, 2001

Group	PY of Observation*	No. of MIs	Rate/100 PY (95% CI)	Incidence Rate Ratio (95% CI)	P-Value
Incidence of MI					
Placebo	949	9	0.95 (0.43–1.80)	0.90 (0.39–2.07)	0.801
Sildenafil, DB	1644	14	0.85 (0.47–1.43)		
Sildenafil, OL	10,859	58	0.53 (0.41–0.69)		
Sildenafil, total	12,503	72	0.58 (0.45–0.72)		
Incidence of all-cause mortality					
Placebo	949	5	0.53 (0.17–1.23)	1.04 (0.35–3.10)	0.945
Sildenafil, DB	1644	9	0.55 (0.25–1.04)		
Sildenafil, OL	10,859	37	0.34 (0.24–0.47)		
Sildenafil, total	12,503	46	0.37 (0.27–0.49)		

CI = confidence interval; DB = double-blind; MI = myocardial infarction; OL = open label; PY = person-years.

* Total number of double-blind patients: placebo = 5054, sildenafil = 6896.

afil.^{28,31,32} In Lowentritt *et al.*,²⁸ 25% of patients exceeded the 100-mg sildenafil dose, and the overall incidence of AEs was the highest of the series (63%). In another study, patients were asked specific, directed questions about the occurrence of AEs rather than open-ended questions, which, in the former case, can result in a bias toward higher reporting.³² Nevertheless, although the above were open-label and not placebo-controlled studies, the rates of discontinuations because of AEs were similar between the case series and placebo-controlled trials, ranging from 0% to 10%, and suggest that AEs experienced in either of these settings are well tolerated and infrequently lead to patient discontinuations.

CARDIOVASCULAR SAFETY OF SILDENAFIL

Although there have been questions about the adverse cardiovascular effects reported among patients taking sildenafil, assuming a causal relation between them may be unwarranted because the interrelations between ED and coronary artery disease are varied and complex. The prevalence of ED and cardiovascular disease are highly correlated with age. Epidemiologic data have shown that the incidence of both conditions increases by a factor of ≥ 3 between the ages of 40 and 70 years.^{39,40} In addition to age and male gender, hypertension, diabetes, dyslipidemia, obesity, and cigarette smoking are shared risk factors for ED and cardiovascular disease.⁴¹ Of the 130 deaths described in the FDA report, approximately 70% of the patients had ≥ 1 of these risk factors.¹ In a recent study of 50 asymptomatic men with ED, 80% had multiple cardiovascular risk factors, and only 15 patients had seen a physician in the preceding 2 years.⁴² Another study has demonstrated a positive correlation between the severity of ischemic heart disease and the extent of ED.⁴³

DOUBLE-BLIND PLACEBO-CONTROLLED TRIALS

In the 18 placebo-controlled trials, the incidence of cardiovascular AEs (other than facial flushing) was 3.0% with sildenafil and 3.5% with placebo treatment. Overall, nearly 80% of all cardiovascular AEs were mild; 16% were moderate, and only 6% were severe among sildenafil-treated patients. This pattern was similar for placebo-treated patients. Discontinuation rates associated with cardiovascular AEs were low and comparable for sildenafil-treated (0.9%) and placebo-treated (0.9%) patients. Similarly, the incidence (per 100 person-years) of cardiovascular serious AEs was comparable between sildenafil-treated (4.1; 95% confidence interval [CI], 2.6 to 5.5) and placebo-treated (5.7; 95% CI, 3.3 to 8.2) patients. The rate of MI was 1.7/100 person-years (95% CI, 0.8 to 2.6) among patients who received sildenafil and 1.4/100 person-years (95% CI, 0.2 to 2.6) among patients who received placebo. None of the serious AEs were considered treatment related.⁴

In the 25-trial subanalysis of patients with ED and other comorbid conditions (ie, diabetes, hypertension, ischemic heart disease), the most commonly reported cardiovascular AE (other than flushing) among all 3 patient subgroups was hypertension (range, 1.2% to 2.5%), none of which were considered treatment related.²³ Treatment-related cardiovascular AEs (eg, palpitations, tachycardia) were experienced by $\leq 1\%$ of all patients, regardless of treatment assignment or comorbid condition. Virtually identical results were obtained in the 35-trial subanalysis. Up to 7% and 4% (both among patients taking ≥ 3 antihypertensives) of sildenafil-treated and placebo-treated patients, respectively, experienced hypertension that was not considered treatment related. Regardless of treatment group or antihypertensive therapy status, $< 1\%$ of all patients experienced treatment-related cardiovascular AEs.²⁴

OPEN-LABEL EXTENSION STUDIES

Many of the patients enrolled in the phase II/III trials had significant comorbid conditions, including hypertension (18%), diabetes (9%), hyperlipidemia (7%), and heart disease (3%).⁵ In the 10 open-label studies, the incidence of cardiovascular serious AEs was 3.5/100 person-years (95% CI, 2.3 to 4.7), and the MI rate was 1.0/100 person-years (95% CI, 0.3 to 1.6); both rates were comparable to their respective counterparts in the aforementioned double-blind studies. Again, none of the serious AEs that occurred during these open-label studies were considered treatment related.⁴

LONG-TERM OPEN-LABEL STUDIES

During the 3-years of open-label treatment, 34 (3.6%) patients discontinued treatment because of AEs involving the cardiovascular system. The largest proportion (1.0%) of patients discontinued because of coronary artery disease, followed by 0.6% of patients who discontinued because of MI. None were assessed by the investigators as being related to treatment. These results are consistent with those originally reported by Morales *et al.*,⁴ in which there were no significant treatment-related cardiovascular AEs, and subsequent discontinuation rates were low and comparable between treatment groups. As mentioned, 119 (12.5%) patients experienced treatment-emergent serious AEs (ie, events occurring within 7 days of the last dose of the study drug, but not necessarily treatment related). The most common were coronary artery disease (2.3%), MI (0.8%), and cardiovascular disease (0.8%). None of the serious AEs were considered related to treatment by the study investigators. A single patient (who had a history of diabetes mellitus and a previous MI) experienced an MI about 20 minutes after intercourse (about 1 hour after taking sildenafil). Although the event was considered unrelated to treatment by the investigator, he and the treating cardiologist concluded that the physical activity associated with intercourse was a contributing factor to the event but its definitive cause could not be determined. The patient was discontinued from the study.

Sildenafil treatment did not increase the rate of MI or other serious cardiovascular events during the 3-year study period. There were 8 acute MIs during the course of the study, which corresponds to an incidence rate of 0.25/100 person-years. This rate is lower than that reported for the clinical safety database and other estimates of MI rates in the United States (see following section). After having an MI, 6 of the 8 patients permanently discontinued the study. A 37-year-old man was temporarily discontinued from the study after hospitalization and quadruple bypass surgery. The condition resolved, and the patient resumed study

medication 3 months after surgery. For 1 other patient who had an acute MI, no action was taken with regard to the study drug. This 75-year-old man had a history of coronary artery disease and had undergone bypass surgery 5 years before the event. The patient had not taken the study drug within 6 weeks of the event. Although he was treated with aspirin and nitroglycerin paste in the emergency department, he was not prescribed nitroglycerin on discharge.

CLINICAL TRIALS SAFETY DATABASE

As of September 30, 2001, Pfizer's clinical safety database contained information on the extent of exposure to sildenafil from 124 completed and ongoing double-blind and open-label clinical trials involving 5054 placebo-treated and 6896 sildenafil-treated patients, representing 2593 person-years of observation.¹⁸ Analysis of these data showed that the overall MI incidence rate was similar in placebo-treated (0.95/100 person-years) and sildenafil-treated patients (0.85/100 person-years; $P = 0.801$). For the open-label studies, analysis of data from patients representing 10,859 person-years of sildenafil exposure demonstrated an MI incidence rate of 0.53/100 person-years. The overall MI rate for double-blind and open-label sildenafil-treated patients was 0.58/100 person-years (Table VI). Similar rates have been reported in a number of epidemiologic studies.⁴⁴⁻⁴⁶

The database also contains (as of September 30, 2001) reports of 5 deaths (from all causes) among double-blind placebo-treated patients and 9 deaths among sildenafil-treated patients. This corresponds to all-cause mortality rates of 0.53/100 person-years and 0.55/100 person-years, respectively ($P = 0.945$). The overall (double-blind and open-label) mortality rate among sildenafil-treated patients was 0.37/100 person-years, which is lower than that (0.66/100 person-years) calculated for men aged 40 to 64 in the United States for 1999.⁴⁷ These results clearly show that the incidences of MI and all-cause mortality among patients who received double-blind and/or open-label sildenafil treatment are similar to those observed among patients who received placebo or in men in the same age cohort of the general population.

POSTMARKETING STUDIES

Much of the concern about the cardiovascular safety of sildenafil has emerged from the publicity surrounding spontaneous reporting of events to the FDA and from case reports that have been published in the literature. As of this writing, we identified 15 published case reports describing cardiovascular AEs associated with the use of sildenafil in 16 patients. Importantly, in 13 of the 15 reports, patients had ≥ 1 risk factor for cardiovascular dis-

TABLE VII. *Studies examining the cardiovascular effects of sildenafil*

Study	Design	n	Patients	Duration	Dosing (mg)	Results
Webb <i>et al.</i> ⁵¹	RCT, crossover	16	Healthy men; men with HTN + amlodipine	Single dose	100 mg S or P + 5–10 mg/day amlodipine	S + amlodipine reduced SBP/DBP (mean maximum change, –8 mm Hg) versus P + amlodipine (–7 mm Hg); S + amlodipine increased HR (2.1 beats/min) versus P + amlodipine (–1.5 beats/min); no synergistic effects of S on amlodipine.
Fox <i>et al.</i> ¹¹	RCT	108	Severe CAD; stable chronic angina	Single dose	100 mg S or P	S did not adversely affect time to limiting angina (10%) and angina (17%) compared with P (5% for both). BP after exercise was similar in the 2 groups; RPP was lower postdrug in S- versus P-treated patients.
Mahmud <i>et al.</i> ¹⁶	RCT, crossover	8	Well-controlled HTN	Single dose	50 mg S or P	S significantly reduced SBP/DBP versus P; mean BP was 17/11 mm Hg less following S versus P. Arterial wave reflection as measured by the augmentation index was reduced in S- versus P-treated patients.
Olsson and Persson ⁷	RCT	224 179	>1 CVD and treatment for CVD (no nitrates)	12 weeks DB; 4–24 weeks OL	50 mg S at start, flexible to 25 or 100 mg	4% and 3% of patients discontinued after S and P, respectively, because of insufficient clinical response. Besides flushing, no treatment-related CV events were reported. In OL, AEs were similar to those in DB: flushing (17%), headache (13%), and dyspepsia (8%).
Patrizi <i>et al.</i> ¹²	RCT, crossover	14	CAD; chronic stable angina with β -blocker	Single dose	50 mg S or P	Neither S nor P reversed the beneficial effects of atenolol (β -blocker) on exercise-induced myocardial ischemia (time to 1 mm ST-segment depression). No differences between S- and P-treated patients in BP and HR at rest or during exercise. No effect of S or P on angina.
Arruda-Olson <i>et al.</i> ¹³	RCT, crossover	105	Known or probable CAD	Single dose	50 or 100 mg S or P	SBP decreased significantly after S versus P; DBP and HR did not change after S. Recovery of BP and HR was similar after S and P. Resting WMSI or ejection fraction did not change after S or P; symptoms of dyspnea or angina were similar after S and P. Echocardiogram interpretations were also similar: normal (15% vs 13%), ischemia (24% vs 26%), infarction (5% both), and infarction with ischemia (56% both).
Pickering <i>et al.</i> ¹⁷	RCT	568	Patients taking 2+ anti-HTNs	6 weeks DB; 6 weeks OL	50 mg S or P to start, flexible to 25 or 100 mg	Incidence of AEs was similar in men taking 2 and 3+ anti-HTNs and placebo; rates were consistent with those previously reported. Less than 2% of patients discontinued because of AEs.

TABLE VII. *Continued*

Study	Design	n	Patients	Duration	Dosing (mg)	Results
Conti <i>et al.</i> ⁸	Retrospective, 11 RCTs	357	IHD, not taking nitrates	4–24 weeks	S (5–200 mg) or P	Incidence of most common AEs was similar in patients receiving S with or without IHD. Incidence of CV events was 5% in IHD and 3% for no IHD patients. Incidence of serious CV AEs in patients with IHD was 7% in S- and 10% in P-treated patients. Most common CV AEs were MI (3% S/P) and unstable angina (2% S/P).
Zusman <i>et al.</i> ¹⁴	Retrospective, 5 RCTs	1685	Patients with ED taking or not taking anti-HTNs	12 or 24 weeks	Treated HTN S/P (25–200 mg) Untreated HTN S/P (25–200 mg)	<i>BP</i> : mean change from baseline in SBP/DBP was –3.6/–1.9 mm Hg after S and –0.8/–0.1 mm Hg after P in patients with treated HTN; mean change was –2.2/–2.0 and –0.1/0.4, respectively, in patients with untreated HTN. Statistically significant differences for some classes of anti-HTNs, but not clinically relevant. <i>HR</i> : mean change was –0.6 beats/min after S and –0.9 after P in patients with treated HTN; mean change was 0.4 and –0.6, respectively, in patients with untreated HTN (NS). Overall incidence of BP-related AEs from all causes was comparable between treated and untreated patients.
Kloner <i>et al.</i> ¹⁵	Retrospective, 18 RCTs	3975	Patients with ED taking or not taking anti-HTNs	6 weeks–6 months	Treated HTN S/P (25–200 mg) Untreated HTN S/P (25–200 mg)	Overall incidence of AEs and BP-related AEs were similar in S-treated patients taking 1+ anti-HTNs (34%) and those not taking anti-HTNs (38%). Number of concomitant anti-HTNs had no effect on the AE profile of S. Discontinuation rates because of all-cause AEs were the same for S-treated patients taking multiple anti-HTNs (2.4%) and those not taking anti-HTNs (2.4%).
Jackson <i>et al.</i> ⁹	Case series	8–12	Healthy men and men with stable IHD	Escalating IV, oral, and IA doses	IV: 20, 40, 80 mg; oral: 100, 150, 200 mg; IA: ≤300 μg/min; IA in IHD: 40 mg	No clinically significant hemodynamic AEs observed after high doses of S in healthy men. In men with IHD, S had a modest effect on hemodynamic parameters in the absence of nitrate therapy.
Hermann <i>et al.</i> ⁵³	Case series	14	Severe CAD	Single dose	100 mg S	Small but significant decreases in arterial BP and pulmonary pressure, systemic/pulmonary vascular resistance, and associated indices. No changes in pulmonary-capillary wedge pressure, right atrial pressure, HR, CO, or CI. Double product decreased significantly. No changes in average peak coronary flow velocity, coronary-artery diameter, coronary flow reserve, etc.

TABLE VII. Continued

Study	Design	n	Patients	Duration	Dosing (mg)	Results
Vardi <i>et al.</i> ¹⁰	Case series	32	Cardiac patients	Single dose	100 mg S	No significant differences attributable to S on SBP or DBP, HR, or double product either at maximum stress or during recovery; S showed small but nonsignificant increase in CO compared with control test.
Vardi <i>et al.</i> ⁵²	Case series	49	Men with and without HTN	Single dose	100 mg S	No significant differences between patients with and without HTN for hypotensive effects of S. Significant reductions in mean SBP (-5.8 mm Hg), DBP (-4.5 mm Hg), and MAP (-5.3 mm Hg) after S ($P < 0.0003$); no effect on HR or double product. Not considered clinically significant.

AE = adverse event; anti-HTNs = antihypertensives; BP = blood pressure; CAD = coronary artery disease; CI = cardiac index; CO = cardiac output; CV = cardiovascular; CVD = double-blind; DBP = diastolic blood pressure; ED = erectile dysfunction; HR = heart rate; HTN = hypertension; IA = intra-arterial; IHD = ischemic heart disease; IV = intravenous; MAP = mean arterial pressure; MI = myocardial infarction; NS = not significant; OL = open-label; P = placebo; RCT = randomized controlled trial; RPP = rate pressure product; S = sildenafil; SBP = systolic blood pressure; WMSI = Wall Motion Score Index.

ease, were being treated for cardiovascular disease, and/or had a previous history of MI or other cardiovascular event before using sildenafil. The cardiovascular events reported after taking sildenafil among these 13 patients included MI (5 patients), ventricular tachycardia (3), cerebrovascular event (2), arteriovenous fistula (1), pulmonary hemorrhage (1), and atrial fibrillation (1). In 3 other case reports, no known history of cardiovascular disease or its risk factors were reported.⁴⁸⁻⁵⁰ However, 1 report stated that a patient who had an MI after taking 100 mg sildenafil had no other risk factors for cardiovascular disease, but later angiography confirmed a 50% stenosis in the left anterior descending artery.⁴⁹ Nevertheless, isolated case reports such as these are of limited value for determining a causal relation between the drug in question and the AE, which is why they contribute little to the clinical safety profile of sildenafil. They do not include control subjects and frequently do not include the interval between the time the dose was taken and the onset of the event. This type of report typically involves unusual cases that cannot be generalized to the patient population at large.

Better controlled studies, such as randomized controlled trials, prospective epidemiologic studies, and large case series, are required to determine if any causal relation exists between sildenafil use and the occurrence of cardiovascular AEs. We identified 14 studies from a search of the literature (which included 4 studies from recently published abstracts) that focused specifically on the cardiovascular-related effects of sildenafil treatment in patient populations with known or probable cardiovascular disease or related conditions. Some of these studies were sponsored, at least in part, by Pfizer; others were conducted by independent investigators. In the ACC/AHA Expert Consensus Document, 2 of the precautions listed (patients taking multiple antihypertensive medications and those with active coronary ischemia) have been addressed in several of these clinical trials, which are summarized by study design in Table VII.^{7-17,51-53}

Because of its modest ability to lower blood pressure, sildenafil has been carefully evaluated in patients with essential hypertension who are taking ≥ 1 antihypertensive. In the second of a 2-part, double-blind, placebo-controlled, crossover study, Webb *et al.*⁵¹ investigated the hemodynamic effects of sildenafil in 16 hypertensive men whose blood pressure was well controlled with the calcium channel antagonist amlodipine. Coadministration of amlodipine and sildenafil reduced blood pressure and increased heart rate compared with placebo and amlodipine (see Table VII for details). Because the changes in blood pressure and heart rate were similar to those observed in healthy men

who received sildenafil alone, these effects were not considered to be synergistic.⁵¹

In a single-blind, randomized, placebo-controlled, crossover study involving 8 men with well-controlled hypertension, Mahmud *et al.* demonstrated that a single 50-mg dose of sildenafil resulted in statistically significant reductions in systolic and diastolic blood pressure and arterial wave reflection relative to placebo. The corresponding raw data for placebo were not provided, making direct comparisons between the 2 treatments difficult. There were no significant changes in heart rate or left ventricular ejection duration after sildenafil. None of the patients complained of hypotensive symptoms.¹⁶

In a post hoc subanalysis of 5 randomized, double-blind, placebo-controlled trials of sildenafil (n = 1685) in which subjects took the study drug the morning of their clinic visit, Zusman *et al.* demonstrated small but statistically significant decreases in blood pressure after sildenafil (−3.6/−1.9 mm Hg) compared with placebo (−0.9/−0.1 mm Hg) among men who were taking concomitant antihypertensive medications.¹⁴ The overall incidence of AEs from all causes and of those related to changes in blood pressure (ie, dizziness, hypotension, syncope) were comparable in patients taking antihypertensives and those not taking antihypertensives for both the sildenafil-treated and placebo-treated groups. In both treatment groups, <1% of all patients experienced an MI, and none of the reports of MI were considered treatment related by the investigators.¹⁴

In a similar retrospective analysis of the 18 double-blind, placebo-controlled trials described in detail above, Kloner *et al.*¹⁵ evaluated the subsets of patients who were taking (n = 1094) and not taking (n = 2881) antihypertensive medication. The incidence of treatment-related AEs among sildenafil-treated patients taking antihypertensives (34%) was similar to the rate among patients not taking antihypertensives (38%). Discontinuation rates because of AEs of all causes were the same for sildenafil-treated patients taking and not taking antihypertensives (2.4%). In addition, the incidence rates of AEs potentially related to blood pressure changes (eg, dizziness, hypotension, hypertension, syncope) were comparable (<2%) in patients taking and not taking antihypertensive medications.¹⁵ In the post hoc analysis of 35 double-blind, placebo-controlled trials, the overall incidence of AEs was 61% in sildenafil-treated patients (n = 1366) taking ≥ 1 of 5 antihypertensive classes (ie, diuretics, β -blockers, α -blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers) and was similar to that reported by sildenafil-treated patients not taking antihypertensives (55%; n = 3453).²⁴

In a case series (n = 49), Vardi *et al.*⁵² assessed the effects of sildenafil (100 mg) on systolic blood pressure, diastolic blood pressure, and mean arterial pressure using ambulatory blood pressure monitoring in normotensive (n = 22) and hypertensive (n = 27) men. Sildenafil produced small but statistically significant changes in mean systolic blood pressure (−5.6 mm Hg), diastolic blood pressure (−4.5 mm Hg), and mean arterial pressure (−5.3 mm Hg, $P < 0.0003$); there were no significant differences between hypertensive and normotensive men in these hemodynamic parameters. Given that there were no associated changes in heart rate or double product (ie, heart rate \times systolic blood pressure), these small reductions in blood pressure were not considered to be clinically significant.⁵² Lastly, in a flexible-dose study of 568 patients, Pickering *et al.*¹⁷ showed that after 6 weeks of double-blind sildenafil or placebo treatment followed by 6 weeks of open-label sildenafil, the occurrence of AEs potentially associated with changes in blood pressure was not different from placebo in patients who were taking 2 (n = 307) or ≥ 3 (n = 222) antihypertensives: hypotension (0.7% sildenafil vs 0% placebo), postural hypotension (0.4% vs 0.4%), and dizziness (2% vs 2%).¹⁷ Together, these data suggest that sildenafil is well tolerated in patients taking concomitant antihypertensives, including those on multidrug regimens.

The other relevant population noted previously in which the cardiovascular effects of sildenafil have been evaluated is men with concomitant ED and ischemic heart disease. In a retrospective subanalysis of 11 trials, Conti *et al.*⁸ demonstrated that the incidences of the most commonly reported AEs (ie, headache, flushing, dyspepsia) among sildenafil-treated patients with ischemic heart disease (n = 237; not taking concurrent nitrates) were similar (25%, 14%, 12%, respectively) to those in sildenafil-treated patients without ischemic heart disease (n = 2103; 21%, 15%, 10%, respectively). Moreover, the incidence of cardiovascular AEs (other than flushing) was comparable in patients with and without ischemic heart disease for both the sildenafil and placebo treatment groups (see Table VII for details).⁸ These results indicate that the safety profile of sildenafil, particularly with regard to cardiovascular effects, is similar in patients with or without concomitant ischemic heart disease.

Patients with ED and comorbid coronary artery disease have been systematically evaluated with regard to the hemodynamic effects of sildenafil treatment. Jackson *et al.*⁹ investigated the acute hemodynamic effects of intravenous sildenafil (40 mg total, administered by 4 infusions) at rest and during exercise in 8 patients with stable ischemic heart

TABLE VIII. Hemodynamic variables at baseline and after oral sildenafil*

Variable	Baseline	After Sildenafil	P-Value
Aortic pressure (mm Hg)			
Systolic	141.6 ± 22.5	132.1 ± 25.4	0.01
Diastolic	75.8 ± 9.6	71.4 ± 10.3	0.01
Mean	100.6 ± 10.6	95.1 ± 12.2	0.01
Pulmonary-capillary wedge pressure (mm Hg)	9.5 ± 2.5	8.9 ± 1.8	0.24
Pulmonary artery pressure (mm Hg)			
Systolic	26.3 ± 4.8	23.9 ± 3.8	0.03
Diastolic	12.6 ± 3.2	11.5 ± 2.6	0.12
Mean	18.1 ± 3.8	16.5 ± 2.6	0.03
Right atrial pressure (mm Hg)	9.2 ± 2.6	9.5 ± 3.0	0.39
Heart rate (beats/min)	66.6 ± 8.3	65.9 ± 9.8	0.63
Cardiac index (L/min/m ²)	2.6 ± 0.5	2.6 ± 0.5	0.74
Systemic vascular resistance index (dyn · sec · cm ⁻⁵ /m ²)	707.6 ± 278.7	684.9 ± 311.6	0.39
Pulmonary vascular resistance index (Wood units/m ²)	0.8 ± 0.3	0.8 ± 0.4	0.63
Heart rate × systolic blood pressure (mm Hg/min)	9435 ± 1739	8641 ± 1722	0.02

* Plus-minus values are mean ± SD. (Reprinted with permission from N Engl J Med.⁵³)

disease and demonstrated small reductions in right atrial pressure, pulmonary arterial occluded pressure, pulmonary arterial pressure, systolic/diastolic systemic arterial pressures, and cardiac output at rest. During exercise, there were similar reductions in these parameters. There were no changes in heart rate after sildenafil either at rest or during exercise. Moreover, there were no treatment-related AEs and no patient discontinued from the study.⁹ Although this intravenous dosage produced plasma concentrations of sildenafil that were 2 to 5 times higher than those following a single, oral dose of 100 mg in healthy volunteers, the hemodynamic response to exercise was preserved in these patients.

Herrmann *et al.*⁵³ evaluated 14 patients with severe coronary artery disease (>70% stenosis of ≥1 coronary artery) and reported that sildenafil produced only small decreases (<10%) in mean arterial and pulmonary arterial pressures and double product. Sildenafil had no effect on pulmonary-capillary wedge pressure, right atrial pressure, heart rate, cardiac output, or cardiac index (Table VIII). Coronary flow reserve (measured after intracoronary adenosine) at baseline was lower in the stenosed arteries (1.3 ± 0.3) than in the reference arteries (2.2 ± 0.4, *P* < 0.05); flow reserve increased about 13% in both stenosed and reference arteries after sildenafil administration (from 1.7 ± 0.6 to 1.9 ± 0.7, *P* = 0.003). All other parameters (eg, average peak velocity, coronary artery diameter, coronary blood flow, coronary vascular resistance) were unchanged. Importantly, the ratio of coronary flow reserve in stenosed versus reference arteries was not affected by sildenafil (baseline, 0.57 ± 0.14; after sildenafil, 0.57 ± 0.15; *P* = 0.90).⁵³

Olsson and Persson⁷ evaluated the safety of sil-

denafil in 224 men with ED and stable cardiovascular disease. Patients were concurrently receiving treatment with β-blockers, angiotensin-converting enzyme inhibitors, and/or calcium channel blockers, but not nitrates. The discontinuation rate for sildenafil-treated patients (7%) was similar to that for placebo-treated patients (9%); 4% of sildenafil-treated and 3% of placebo-treated patients stopped treatment because of an insufficient clinical response. Only 1 patient in the placebo group withdrew because of an AE. The incidence rates of the most commonly reported AEs were also comparable between the sildenafil-treated and placebo-treated groups: flushing (17% vs 2%), headache (15% vs 1%), and dyspepsia (5% vs 0%). No serious AEs were reported; moreover, with the exception of facial flushing, no cardiovascular AEs were reported.⁷

A number of studies have also used exercise and/or stress tests to evaluate the effects of sildenafil in patients with coronary artery disease. Vardi *et al.*¹⁰ used a treadmill test to evaluate the effects of sildenafil on blood pressure, heart rate, and double product during pretest, maximum stress, and recovery in cardiac patients. The results were compared with a control test conducted before sildenafil (100 mg) administration. There were no significant differences between the control and sildenafil tests for any of the monitored parameters.¹⁰ In a randomized, double-blind, placebo-controlled crossover trial, Patrizi *et al.*¹² evaluated the effects of sildenafil (50 mg) treatment on exercise-induced myocardial ischemia in 14 patients with coronary artery disease and who were taking the β-blocker atenolol. Neither sildenafil nor placebo interfered with the beneficial effect of atenolol on exercise-induced ischemia, and there were no differences between baseline and peak exercise values

for blood pressure or heart rate after sildenafil. Furthermore, no patient experienced AEs, such as headache or facial flushing, after sildenafil or placebo administration.¹² More recently, in an exercise study, Fox *et al.*¹¹ demonstrated that sildenafil treatment (100 mg) did not adversely affect time to limiting angina, blood pressure, or heart rate in patients with severe coronary artery disease and ED during a treadmill stress test. The mean energy expenditure in both groups was 8 metabolic equivalents of oxygen consumption (METS), which is considerably greater than the energy expended by most people even during vigorous sexual activity (5 to 6 METS).^{54,55} Lastly, Arruda-Olson *et al.*¹³ recently demonstrated in an independent (non-Pfizer-sponsored), randomized, double-blind, placebo-controlled, crossover trial that sildenafil (50 or 100 mg) did not affect the onset, extent, or severity of exercise-induced ischemia in 105 men with stable coronary artery disease. These data provide further support for current treatment guidelines (see next section) stating that sildenafil is well tolerated among patients with stable coronary artery disease who are not taking nitrates, which is the only absolute contraindication to sildenafil.⁶

SUMMARY OF GUIDELINES AND RECOMMENDATIONS FOR THE USE OF SILDENAFIL AMONG PATIENTS WITH CARDIOVASCULAR DISEASE

A number of consensus statements and practice guidelines have been published on the management of ED in patients with cardiovascular disease. The ACC and AHA used both published and unpublished data (provided by Pfizer Inc) to develop their Expert Consensus Document, which provides recommendations for the use of sildenafil in cardiac patients with ED based on the stratification of patients into 3 categories: (1) those at clinical risk, (2) those with acute ischemic syndromes, and (3) patients who inadvertently take nitrates while also taking sildenafil.⁶ Specific ACC/AHA recommendations are summarized in Table IX. There are 2 other consensus statements—1 from the United Kingdom, the other from the United States—that also provide management recommendations based on the stratification of patients into low-, intermediate-, and high-risk categories^{54,55} (see Table IX). Most patients with cardiovascular disease are categorized as low risk and can safely initiate/resume sexual activity or receive sildenafil treatment for ED. With the exception of nitrates, there are no other contraindications for sildenafil with other cardiovascular medications.⁵⁴ Patients at intermediate risk should receive further cardiovascular evaluation before re-stratification into either the low-risk or high-risk group. Patients at high risk

should be stabilized with treatment before resumption of sexual activity or initiation of any treatment for ED. In any case, treatment of ED in patients with cardiovascular disease is always secondary to stabilizing their cardiovascular status and optimizing drug therapy for cardiovascular symptoms.^{54,55} The documents clearly state that “sildenafil and other ED treatments do not increase a patient’s cardiovascular risk and are effective in managing ED in patients with diagnosed cardiovascular disease.”⁵⁴ There are 3 additional consensus documents, 1 each from Canada, Israel, and Australia. Compared with the aforementioned statements, these documents appear to be more stringent in categorizing patients with cardiovascular disease or those at risk for cardiovascular disease who should not take sildenafil for ED (see Table IX for details). In general, however, the published recommendations make it clear that with the exception of patients with ED who are taking nitrates, nearly all patients can safely take sildenafil for ED if an appropriate cardiovascular risk assessment has been performed and proper clinical direction is followed.

OCULAR SAFETY AND SILDENAFIL

Although sildenafil is a potent and selective inhibitor of PDE5, it also has an approximately 10-fold lower affinity for PDE6, which is present in high concentrations in the retinal photoreceptors.²⁰ Given that PDE6 is a key enzyme in the phototransduction cascade, the overall safety of sildenafil in the visual system has been extensively evaluated in preclinical and clinical trials during the drug’s development and in other well-designed studies conducted after sildenafil was approved for marketing. (Patients with retinitis pigmentosa were excluded from clinical trials.) Our electronic searches of the literature (1995 to the present) identified 17 of these studies (n = 5742). The results of these studies are summarized in the following sections.

CLINICAL STUDIES

From the reports of fixed-dose studies, the incidences of all-causality and treatment-related abnormal vision were dose related, from 1.0% at 25-mg doses, to 2.2% at 50-mg doses, to 11.1% at 100-mg doses of sildenafil for visual AEs from all causes and from 0.3% to 1.6% to 10.7%, respectively, for treatment-related AEs^{4,59} (Table X). Most visual AEs were mild or moderate in severity. Severe AEs have been reported by 5 patients: 1 occurred after 25 mg of sildenafil and was not considered treatment related (ie, change in color perception); 4 occurred after supratherapeutic doses (200 mg) of sildenafil and were considered treat-

TABLE IX. Summary of consensus statements and clinical guidelines on the use of sildenafil in patients with cardiovascular disease

Developer and Date	Type of Document (Location)	Purpose	Evidence Base	Recommendations
ACC/AHA, 1999 ⁶	Expert consensus (United States)	To inform practitioners, payers, and other interested parties in areas in which rigorous evidence is not yet available	Published data on sildenafil and unpublished data provided by Pfizer Inc.	<p>A. Use is contraindicated:</p> <ol style="list-style-type: none"> 1. Concurrent use of nitrates <p>B. CV effects potentially hazardous in patients:</p> <ol style="list-style-type: none"> 1. With active coronary ischemia, not taking nitrates 2. With CHF and borderline low BP with borderline low volume 3. On complicated, multidrug anti-HTN program 4. Taking drugs that can prolong the half-life of sildenafil
Multidisciplinary panel of physicians and surgeons, 1999 ⁵⁴	Consensus statement (United Kingdom)	To provide practical advice on the management of ED, specifically in patients with CVD, and address assessment of CV risk in restoring sexual activity in these patients	Available evidence or consensus of opinion when no data are available	<p>Risk assessment algorithm based on graded risk:</p> <p>Low:</p> <ul style="list-style-type: none"> Controlled hypertension Asymptomatic <3 CAD risk factors (not age or gender) Mild valvular disease or mild stable angina Post successful revascularization * Uncomplicated post MI (>6–8 wks) * LVD/CHF (NYHA Class I) <p>Intermediate:</p> <ul style="list-style-type: none"> Recent MI or CVA (≤6 weeks) ≥3 risk factors for CAD, excluding age and gender LVD/CHF (NYHA Class I, II) Murmur of unknown cause Moderate stable angina <p>High:</p> <ul style="list-style-type: none"> Unstable or refractory angina Uncontrolled HTN (SBP >180 mm Hg) CHF (NYHA Class III, IV) Recent MI or CVA (≤14 days) High-risk arrhythmias Hypertrophic cardiomyopathy Moderate/severe valve disease
International consensus conference, 2000 ⁵⁵	Consensus recommendations (United States)	To provide clinically useful guidelines for the assessment of cardiac risk associated with sexual activity and for the management of sexual dysfunction in patients with CVD or risk factors for CVD	Presentations on epidemiology, pathophysiology, pharmacology, and psychosocial mechanisms of sexual activity and cardiac risk	

TABLE IX. *Continued*

Developer and Date	Type of Document (Location)	Purpose	Evidence Base	Recommendations
HSFC/CCS, 2000 ⁵⁶	Statement (Canada)	To help physicians make treatment decisions concerning sildenafil in patients with CVD and ED	7-member panel of volunteers from both organizations	Decision tree: Should patients be considered for sildenafil treatment? No: Nitrate therapy prescribed and used Symptomatic hypotension from any cause Patients who may need nitrates (acute coronary syndromes, active ischemia, angina during intercourse) Maybe: Asymptomatic hypotension Aortic stenosis or LVOT disease NYHA Class III or IV Yes:
IHS, 2000 ⁵⁷	Expert consensus (Israel)	To represent the current knowledge on the safety of sildenafil in cardiac patients	IHS committee	All others Sildenafil is permitted for: Patients with stable CVD (post-MI, after bypass surgery) Stable angina Sildenafil should not be given to patients: Taking nitrates With labile and difficult-to-control HTN With low BP With uncontrolled heart failure and/or low BP being treated with a combination of vasodilators and diuretics
Chew <i>et al.</i> , 2000 ⁵⁸	Recommendations (Australia)	To examine association between sildenafil and spontaneous death reports so that the nature/degree of risk can be identified and proper guidelines can be developed	Published evidence	Algorithm for using sildenafil in the management of ED: Sildenafil can be used if the patient is fit, there is no CVD, and the patient does not require nitrate therapy

ACC = American College of Cardiology; AHA = American Heart Association; Anti-HTN = antihypertensive; BP = blood pressure; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; ED = erectile dysfunction; HSFC = Heart and Stroke Foundation of Canada; HTN = hypertension; IHS = Israel Heart Society; LVD = left ventricular dysfunction; LVOT = left ventricular outflow tract; MI = myocardial infarction; NYHA = New York Heart Association; SBP = systolic blood pressure.

* Applies only to US guidelines.⁵⁵

TABLE X. Visual adverse events and discontinuations in double-blind, placebo-controlled trials*

	Fixed Dosing						Flexible Dosing	
	Placebo	Sildenafil					Placebo	Sildenafil (25–100 mg)
		—	5 mg	25 mg	50 mg	100 mg		
Evaluable patients (n)	607	86	312	511	506	191	725	734
Adverse events								
All causality (%)	0.5	0.0	1.0	2.2	11.1	43.5	0.4	2.7
Treatment related (%)	0.3	0.0	0.3	1.6	10.7	41.9	0	1.9
Serious adverse events (n)	0	0	1	0	0	4		
Discontinuations (n)	0	0	0	0	1	1	1	0

* Study reports from 12 phase II/III clinical trials. (Adapted from data on file.⁵⁹)

ment related (ie, blurred vision, “flashing lights,” “blue haze,” change in color perception). All events were coincident with peak plasma concentrations of sildenafil and were transient and fully reversible. None persisted >6 hours after taking sildenafil. Within the therapeutic dosing range (ie, 25 mg to 100 mg), only 1 patient discontinued treatment solely because of abnormal vision. There were no serious visual AEs. In the flexible-dose series, 2.7% of sildenafil-treated and 0.4% of placebo-treated patients reported abnormal vision (eg, “blue haze” around objects, decreased color discrimination, increased brightness of light).⁵⁹ Overall, results from phase I/II/III acute treatment studies have demonstrated that there are mild, transient, and reversible changes in blue/green color discrimination. Most of these changes were associated with supratherapeutic doses and coincided with peak plasma concentrations of sildenafil.

A number of acute studies have evaluated the effects of sildenafil on visual function using a variety of tests for acuity (Snellen), color discrimination (Farnsworth-Munsell [FM] 100-hue), contrast sensitivity (Pelli-Robson), electroretinograms, and photostress testing. In 1 study, a single supratherapeutic dose (200 mg) of sildenafil administered to 8 healthy subjects had no clinically significant effects on visual function, although there were small, transient changes in FM 100-hue scores.⁶⁰ In a subsequent flexible-dosing (50 mg to 200 mg) study, 16 healthy male volunteers showed significant changes in FM 100-hue scores in the blue-green range with the 100-mg and 200-mg sildenafil doses at 1 and 2 hours after dosing; these changes were mild and transient.⁶¹ There were no long-term consequences (up to 52 weeks) with acute sildenafil administration or PRN treatment (up to 40 weeks) on visual function tests.^{60,61} In a placebo-controlled trial of single, flexible sildenafil dosing (10 mg to 150 mg), Yajima *et al.*⁶² reported no effects on intraocular pressure or pupil size in healthy male subjects receiving sildenafil or placebo.

In long-term, open-label studies of up to 2 years in duration, the overall incidence of abnormal vision AEs remained low (2%). Events were described as predominantly minor color tinge to vision and increased sensitivity to light or blurred vision.⁵ There were no cumulative structural changes or changes in visual function.^{4,63,64} Moreover, no patients discontinued because of visual AEs, even after 2 years of extended treatment.⁶⁴ Longer-term results showed that after up to 4.5 years of exposure to sildenafil, patients reported only 4 (<1%) occurrences of visual disturbances and 1 (0.1%) case of conjunctival infection. All 5 visual AEs were considered treatment related. The overall incidence of visual AEs was lower than those reported for the parent trials and initial open-label studies because we included only those AEs that resulted in a dose change or discontinuation. Only 1 patient discontinued because of a non-treatment-related visual AE (ie, a retinal vein occlusion in the left eye with no temporal association with sildenafil dosing). There were no serious AEs involving the visual system. Thus, with up to 4.5 years of sildenafil treatment, the occurrence of significant visual events has remained low.

POSTMARKETING CASE SERIES AND REPORTS

As of this writing, 9 case reports have been published describing adverse visual events associated with sildenafil use. Donahue and Taylor⁶⁵ described a patient with a 50-year history of tobacco abuse and preexisting vascular disease who experienced a pupil-sparing third nerve palsy after taking a 50-mg dose of sildenafil. Tripathi and O'Donnell⁶⁶ reported on a patient with no known risk factors for systemic vascular disease who had a superotemporal branch retinal artery occlusion after taking a 100-mg dose of sildenafil. Gabrieli *et al.*⁶⁷ evaluated a patient with glaucoma and a 10-year history of treated hypertension, and attributed visual halos after a 100-mg dose of sildenafil to a higher rod response to light stimuli (higher sensitivity) as reflected in decreased electroretinogram wave amplitudes (0.14 log units) at 2 hours after

dose. Smith *et al.*⁶⁸ described a patient who experienced a pulsating blue light in the central visual field of his right eye. The patient had a history of diplopia, proptosis, and amblyopia. In addition, he had had a hemicolecotomy for carcinoid tumor 10 years before this event. The causality of the ocular/visual AE in each of these cases is undetermined.

Most recently, Pomeranz *et al.*⁶⁹ described 5 patients who developed nonarteritic anterior ischemic optic neuropathy (NAION) after taking sildenafil: 3 of the patients developed NAION after using sildenafil for the first time; 2 others had been using sildenafil periodically for 1 to 2 years. All 5 patients had optic discs with a small cup-to-disc ratio (eg, 0.1). This anatomic configuration is more common in patients with NAION and has been implicated in the pathogenesis of the neuropathy.^{70,71} Burde⁷² referred to this anatomy as a “disc at risk.” The investigators acknowledged that a definite causal relation between sildenafil and NAION cannot be established given the large number of prescriptions that have been written for sildenafil and the overlap in the patient populations that are at risk for NAION who are also likely to be taking sildenafil, making attribution of these types of events difficult to evaluate. Moreover, these reports are infrequent and the condition is relatively common in those >60 years of age. Thus, to reasonably attribute cause requires the appearance of a clear “signal,” or pattern of clinical events related to sildenafil that exceeds the background incidence of similar events in the absence of sildenafil use. To date, no clear signal of serious pathology has emerged for sildenafil.⁷³

Other case series and controlled studies in healthy volunteers have shown that sildenafil has no significant effects on visual acuity, color perception, and intraocular pressure.^{74–76} There have been conflicting results for effects on ocular blood flow. In a randomized, placebo-controlled, crossover study involving 15 healthy male volunteers and using laser Doppler flowmetry, Grunwald *et al.*⁷⁷ found no significant changes in mean foveolar choroidal or optic nerve blood flow when subjects who received sildenafil (100 mg) were compared with those who received placebo. This study was powered to detect a 20% change in blood flow with 90% confidence. By contrast, 2 case series reported significant changes from baseline after single oral doses of sildenafil (50 mg) in healthy male volunteers. Sponsel *et al.*,⁷⁸ using a derived measurement, found a 29% increase in ocular pulsatile choroidal blood flow after sildenafil ($n = 12$; $P = 0.02$). Dündar *et al.*⁷⁹ found statistically significant increases in peak systolic, end-diastolic, and mean flow velocities of the ophthalmic artery ($n = 14$; $P < 0.05$). Thus, although these studies differed in their conclusions on the effects on ocular blood

flow, their results indicate that sildenafil treatment does not cause a decrease in optic nerve head or choroidal blood flow. Although studies have shown modest and reversible effects on electroretinograms, the results have been inconsistent across trials^{75,80} and have not been considered clinically relevant⁸¹ (Table XI).^{4,60–64,74–80,82–87} In terms of special patient populations, there have been no reports of increased visual AEs in patients with pre-existing eye disorders, including diabetic neuropathy,⁸² glaucoma,^{82,87} and macular degeneration.^{76,82} Taken together, these studies support the conclusion that there is no evidence that sildenafil—even after >4 years of treatment—produces any permanent changes to the visual system or leads to an increased risk of vascular events in the eye. To date, there is no evidence that the incidence of vascular events is greater than that observed in the general population of men with similar demographic characteristics.⁸⁸

CONCLUSION

Numerous controlled clinical trials have established that sildenafil has an excellent overall safety profile. The AEs occurring among sildenafil-treated patients are generally transient and mild to moderate in severity, even among men with comorbid conditions such as diabetes, hypertension, and depression. AEs rarely lead to treatment discontinuation under these controlled conditions. Long-term, open-label studies have demonstrated that sildenafil continues to be well tolerated for >4 years with no increase in the incidence or severity of AEs. Independent postmarketing case series confirm and extend these findings.

To date, sildenafil has been approved in >110 countries around the world. Nearly 600,000 physicians have written >100 million prescriptions for sildenafil to treat ED in >20 million men worldwide. Despite the increasing evidence demonstrating its overall safety, physicians and patients alike continue to have concerns about the risk of cardiovascular AEs after taking sildenafil. ED and cardiovascular disease share a number of risk factors,⁴¹ and the incidence of ED and cardiovascular disease increases substantially with age.^{39,40} Therefore, patients who are taking sildenafil for ED are likely to be at increased risk for cardiovascular events *independent* of their taking the drug. Recent studies of sildenafil in patients with cardiovascular disease have shown no change in exercise tolerance and no worsening of ischemia during exercise testing. In both placebo-controlled and open-label studies, there was no increase in MI rates or all-cause mortality rates in patients receiving sildenafil. Studies have shown that sildenafil is well tolerated, and has minimal cardiovascular effects and AEs in ED pa-

TABLE XI. Summary of studies assessing visual safety and function

Study	Design	n	Population(s)	Assessment	Results
Clinical:					
Phase I/II/III acute studies					
Laties <i>et al.</i> ⁶⁰	Case series	8	Healthy volunteers	Visual function	A single supratherapeutic 200-mg dose of S produced no clinically significant effects on visual field, acuity, photostress test, IOP, or ERG.
Morales <i>et al.</i> ⁴	RCT, 4–24 weeks	2722	Men with ED	Visual AEs	Dose-related visual AEs; higher incidence (11%) at 100 mg S; most common AE was mild and transient color tinge to vision.
Laties <i>et al.</i> ⁶¹	RCT, 12 weeks, crossover	16	Healthy volunteers	Color discrimination (FM 100-hue)	Statistically significant changes in FM 100-hue scores 1–2 hours after 100 or 200 mg S; changes were reversible, mild, and coincided with peak plasma concentrations of S.
Yajima <i>et al.</i> ⁶²	PC	16/48	Healthy volunteers	IOP; pupillometry	No effect on IOP or pupil size in patients receiving S or P.
Long-term studies					
Laties <i>et al.</i> ⁶⁰	OL, 40 weeks	47	Men with ED	Visual function	No clinically significant changes in acuity, contrast sensitivity, photostress test, or slit-lamp examination; no visual SAEs or discontinuations because of visual AEs.
Morales <i>et al.</i> ⁴	OL, ≤18 months	2199	Men with ED	Visual AEs	Low incidence (2%) of abnormal vision (minor, transient, color discrimination).
Grunwald <i>et al.</i> ⁸²	Retrospective, 18 RCTs	66	Men with eye disorders	Visual AEs	14% of S-treated patients had visual AEs; only 1 discontinued because of visual AE.
Laties <i>et al.</i> ⁶¹	OL, 40 weeks	47	Men with ED	Color discrimination (FM 100-hue)	No clinically significant changes in FM 100-hue test at 12 or 52 weeks compared with baseline measurements.
Laties <i>et al.</i> ⁶³	OL, 9 months	435	Men with ED	Visual AEs	14% of patients reported visual AEs after S; transient changes in color vision, blue tinge to vision, increased sensitivity to light, transient halo effects; no visual SAEs.
Zrenner <i>et al.</i> ⁶⁴	OL, ≤2 years	31	Men with ED	Visual function	No clinically significant changes in acuity, color discrimination, contrast sensitivity, photostress test, or slit-lamp examination after S; no discontinuations because of visual AEs.
Postmarketing:					
Clinical safety studies					
Kretschmann <i>et al.</i> ⁷⁴	Case series	6	Men with ED	Visual function	After 100 mg S, no change in acuity, perimetry, amplitude/timing of photopic responses; slight changes in stereopsis, color test errors, full-field ERG, implicit times in multifocal ERG.

TABLE XI. *Continued*

Study	Design	n	Population(s)	Assessment	Results
Vobig <i>et al.</i> ⁷⁵	Case series	5	Healthy volunteers	Acuity, visual field, color, IOP, ERG, VEP	No significant effects of S on acuity, visual field, color perception, IOP, or VEP; no reported visual AEs after 100 mg S; significant ERG reductions resolved within 6 hours.
Jägle <i>et al.</i> ⁸³	RCT	20	Healthy volunteers	Visual function	Statistically significant increases in sensitivity during tritanopia and prolonged implicit times of ERGs; no change in ERG amplitude; no visual AEs; all visual parameters returned to normal range within 24 hours.
Jägle <i>et al.</i> ⁸⁴	Case series	2	Healthy volunteers	Visual function	Dose-dependent, transient prolongations in ERG implicit times and amplitude; no reported visual AEs.
Sponsel <i>et al.</i> ⁷⁸	Case series	12	Healthy adults	Visual function	Significant increases in ocular blood flow (29%), contrast sensitivity (34%), and retinal microcirculation (8%) after 50 mg S; no changes in SBP/DBP, pulse amplitude, or IOP.
Grunwald <i>et al.</i> ⁸⁷	RCT, crossover	15	Glaucoma	IOP	At maximum therapeutic dose (100 mg), S did not produce any significant acute change in IOP in patients with chronic glaucoma.
Grunwald <i>et al.</i> ⁷⁷	RCT, crossover	15	Healthy males	Ocular circulation	No significant change in BP, IOP, or optic blood flow parameters in S-treated patients compared with P-treated patients.
Luu <i>et al.</i> ⁸⁰	Pseudo-PC	18	Healthy volunteers	Visual function	Statistically significant increase in number of color vision errors after S versus no drug; small but significant changes in ERG, but all were still within normal limits.
McCulley <i>et al.</i> ⁸⁵	RCT	8	Healthy volunteers	HVF	Most (80%) subjects had no detectable changes in blue-on-yellow or white-on-white HVF after 200 mg S.
Birch <i>et al.</i> ⁷⁶	RCT, crossover	9	Macular degeneration	Visual function (several tests)	No acute changes in visual acuity, color perception, or photostress test; no visual AEs.
Dündar and Ozkan ⁷⁹	Case series	14	Healthy male volunteers	Ocular hemodynamics	Significant increases from baseline in PSV (42.1 ± 7.3), EDV (13.6 ± 4.5), and MV (22.0 ± 5.8) after S (50 mg; 50.5 ± 15.1 , 18.5 ± 5.6 , 27.8 ± 9.0 , respectively); no change in IOP, SBP/DBP; significant increase in HR ($P < 0.05$).
Pache <i>et al.</i> ⁸⁶	Case series	10	Healthy subjects	Retinal vasodilation	Significant increase in retinal arterial (5%) and venous (6%) diameter at 1 hour after 50-mg dose S; S produced mild but significant reduction in BP and increase in HR; no change in IOP.
Spontaneous reports Yajima <i>et al.</i> ⁶²	Safety database	36	Patients with glaucoma/high IOP	IOP, pupillometry	No patients with glaucoma showed worsening of disease; 8% had visual AEs.

AEs = adverse events; BP = blood pressure; DBP = diastolic blood pressure; ED = erectile dysfunction; EDV = end-diastolic velocity; ERG = electroretinogram; FM = Farnsworth-Munsell; HR = heart rate; HVF = Humphrey visual field; IOP = intraocular pressure; MV = mean velocity; OL = open-label; P = placebo; PC = placebo-controlled; PSV = peak systolic velocity; RCT = randomized, controlled trial; S = sildenafil; SAEs = serious adverse events; SBP = systolic blood pressure; VEP = visual evoked potentials.

tients with ischemic heart disease and in those taking multiple antihypertensive medications. Sildenafil is contraindicated only for patients taking nitrates, and this is clearly delineated in the product label. Thus, physicians should ensure that the patient is not taking nitrates or has discontinued nitrate treatment before prescribing sildenafil.

Given the slight inhibitory affinity of sildenafil for PDE6, concerns have also been raised about potentially adverse effects on the visual system. Results from clinical trials and postmarketing experience have shown slight changes in color vision, a "blue haze" around objects, and an increased sensitivity to light that are mostly associated with higher doses of sildenafil. Again, these events are transient, fully reversible, and rarely lead to treatment discontinuation. Reports of serious visual events from PDE5 inhibition, such as NAION, have appeared sporadically; however, it has not been shown that their incidence exceeds that in the general population of men who share the same demographic characteristics as those taking sildenafil for ED. Thus, existing evidence indicates that sildenafil is not associated with significant structural or functional alterations to the visual system.

Published clinical guidelines and consensus statements provide practical advice on the management of ED, particularly among patients with cardiovascular disease or its associated risk factors. Detailed algorithms can assist practitioners in this assessment and in subsequent treatment decisions. If the treating physician performs a comprehensive clinical evaluation that includes a physical examination, detailed medical (and medications) history, and an assessment of cardiovascular risk,⁵⁵ most patients presenting with ED can be safely and effectively treated with sildenafil.

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