Efficacy and Safety of Sildenafil Citrate for Treatment of Erectile Dysfunction in a Population With Associated Organic Risk Factors

ANDRÉ T. GUAY,* JESUS B. PEREZ,* JERILYNN JACOBSON,† AND ROBERT A. NEWTON‡

*From the *Department of Endocrinology and the †Department of Biostatistics, Lahey Clinic, Peabody, Massachusetts; and ‡New England Andrology, Urology Section, Reading, Massachusetts.*

ABSTRACT: The objective of this study was to determine the efficacy and safety of sildenafil in patients with erectile dysfunction (ED) and associated organic risk factors in a multispecialty clinic. Patients (n = 521) were diagnosed with ED based on self-assessment. Associated risk factors were managed by medication or lifestyle modifications, or both, before treatment with sildenafil for ED. Patients received a 50-mg dose of sildenafil that could be adjusted to 100 mg or 25 mg based on tolerability and efficacy. Patients recorded the number of successful intercourse encounters for 6 to 8 weeks, and the number of adverse events. Overall, there was an 82% successful intercourse rate with sildenafil treatment. The predominant associated risk factors for ED were hypertension (39%), hypogonadism (37%), and multiple medications (34%). Common adverse events due to sildenafil treatment were mild to moderate in nature and resulted in <2% patient discontinuation. Clinicians should be particularly careful to evaluate patients presenting with ED because the condition can be accompanied by a wide spectrum of risk factors requiring monitoring and treatment. However, with adequate treatment and control of these risk factors, the use of sildenafil in a representative population of men with ED in a multispecialty clinic can achieve a higher efficacy rate than previous studies have indicated.

Key words: Hypogonadism, medication/lifestyle modifications.

J Androl 2001;22:793–797

Erectile dysfunction (ED) is a mutifactorial condition affecting 1 out of 10 men in the United States (Jackson et al, 1999). Its etiology can be organic, psychogenic, or most commonly, derived from a combination of the two (Lue, 2000).

Medical risk factors include diabetes, cardiovascular conditions (eg, hypertension, hypercholesterolemia, atherosclerosis, and a recent history of myocardial infarction), pituitary/gonadal dysfunction, anemia, and renal/hepatic failure (Benet et al, 1994). Psychogenic causes can include depression and anxiety (Lue, 2000). In addition, medications may be a causal factor; approximately 25% of cases of ED are caused by either prescription or over-the-counter medications (O'Keefe and Hunt, 1995; American Association of Clinical Endocrinologists [AACE], 1998). Drugs used socially such as nicotine, alcohol (in excess), and other recreational drugs also increase the prevalence of organic ED (Benet et al, 1994). Finally, studies have shown that the prevalence of complete ED

rises with advancing age, from 5% in men aged 40, to 15% in men aged 70 (Feldman et al, 1994).

The multiplicity of potential causes and contributors heightens the importance of a comprehensive clinical evaluation. Guidelines from the National Institutes of Health (NIH) specify that an examination for ED should include a detailed medical and sexual history, a physical examination, a psychosocial assessment, and basic laboratory studies, which may include an endocrine evaluation (NIH Consensus Development Panel on Impotence, 1993). AACE (1998) has also developed an algorithm showing treatment pathways for various risk factors.

Previously published reports from clinical practice settings show significant improvement with treatment of sildenafil citrate (Viagra, Pfizer, Inc, New York, NY) for patients with ED (Jarow et al, 1999; Marks et al, 1999). Although these reports on the success of sildenafil included patients with broad-spectrum ED, specific criteria excluded patients with an uncontrolled medical illness, receiving specific medications, low serum testosterone levels, and alcohol or drug dependence.

Our study examined patients with ED at a multispecialty clinic who presented with conditions that were generally excluded by earlier studies. Our goal was to assess the safety and efficacy of sildenafil in a broad spectrum of patients routinely encountered by clinicians.

Methods

Patients were diagnosed with ED based on self-assessment and were eligible for inclusion in the study if ED was of at least 6 months' duration and the failure rate of intravaginal intercourse was at least 50%. This is double the failure rate of 25% of sexual attempts in men without ED (Masters et al, 1988). Other inclusion criteria were a relationship with a female partner and no previous use of sildenafil. Exclusion criteria included concurrent use of nitrates and failing a cardiac stress test, as indicated by the American College of Cardiology/American Heart Association (Cheitlin et al, 1999). A complete medical and psychological profile was completed on each patient prior to their entering the study.

Statistical Analyses

A binomial test of independent proportions was used to determine statistically significant differences in rates of success versus failure within patient groups. Chi-square analyses (or the Fisher exact tests when appropriate) were used to compare success rates between hypogonadal groups. Finally, tests of linear and polynomial contrasts were used to detect trends of success concomitant to increasing age (measured in ordinal categories). Analyses were conducted using SPPS statistical software for Windows, version 9.0 (SPPS Inc, Chicago, Ill).

Medication Changes

Medical and drug histories of patients were retrieved from the clinic database. Patients were instructed to change or stop taking any over-the-counter and prescription drugs believed to interfere with sexual functioning (AACE, 1998). For example, patients taking lipid-soluble beta-blockers such as metoprolol or propanolol, which aggravate sexual function, were switched to atenolol, which has a much smaller negative effect. Patients with hypertension were considered for a switch to an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. A substitution with one of the statin class of drugs was considered for patients taking lipid-lowering drugs such as gemfibrozil.

Lifestyle Modifications

Smokers were encouraged to quit. Roughly 75% of patients reduced their cigarette intake to between ½ and 1 pack per day from approximately 2 packs per day. They were encouraged not to smoke for several hours before taking sildenafil. About 50% of patients used nicotine patches, which are not a risk for sexual dysfunction (Guay et al, 1998). None of the patients studied quit smoking entirely.

Some men who had a history of drinking alcohol in excess, defined as more than the 2 drinks per day considered a moderate amount, were asked to decrease their intake. (A drink is defined as one 12-ounce beer, 5 ounces of wine, or 1.5 ounces of 80-proof alcohol.) However, some patients were still ingesting more than 2 drinks per day. Although they were encouraged to limit alcohol intake to 1 drink on the days when sildenafil was used, compliance was not monitored by the investigator.

Use of recreational drugs was entirely discouraged. Better dietary adherence was recommended for patients with diabetes or hyperlipidemia.

Hormonal Assessment

Estimates of hypogonadism as a causative factor in ED range from 7% to 35% (Braunstein, 1983; Nickel et al, 1984; McClure, 1988; Govier et al, 1996); it can be primary or secondary to conditions such as myocardial infarction, sepsis, respiratory failure (Zonszein, 1995), diabetes, sleep apnea, and aging (NIH Consensus Development Panel on Impotence, 1998). Although the recommended treatment of such ED risk factors as diabetes and hypertension is quite well established, debate has surrounded the assessment and treatment of hypogonadism. Some research has indicated that declines in libido or testis atrophy were predictive of hypogonadism and precluded the need for laboratory testing. However, a 1995 study by Govier et al (1996) of 508 patients did not find these conditions predictive, and most experts have recommended endocrine screening (Nickel et al, 1984; NIH Consensus Development Panel on Impotence, 1993; Govier et al, 1996). Given this, patients whose profiles indicated a possibility of hypogonadism had their serum levels of unbound testosterone measured by radioimmunoassay (Diagnostic Products Corp, Los Angeles, Calif). Patients with free testosterone levels below age-related ranges were given a testosterone supplement or had their endogenous testosterone levels increased by the fertility drug clomiphene citrate. Serum prolactin levels were also measured by radioimmunoassay (Dupont, Boston, Mass). Patients with a prolactin level of >15 ng/mL were treated with dopamine agonists.

Men with known hypogonadism were treated with testosterone replacement therapy for 3 months. If this treatment was not successful in treating their ED, sildenafil was added as a treatment.

Some men received sildenafil treatment before the results of their testosterone levels had returned from the laboratory, and thus before the diagnosis of hypogonadism could be made. This group (n = 44) had from slightly low to low testosterone. Their response to sildenafil prior to any testosterone treatment was noted. This offered us a chance to compare the effects of sildenafil in these men to the men with known hypogonadism (n = 108), who had the benefit of at least 3 months of testosterone treatment.

Dosage

Patients were prescribed a minimum of four 50-mg tablets and a maximum of 10. They were instructed to take a 50-mg dose of sildenafil at least twice a week, approximately 1 hour before sexual activity, but not more than once within a 24-hour period. Dosage could be increased to 100 mg or decreased to 25 mg based on tolerability and efficacy. Patients were considered nonresponders if they could not satisfactorily complete intravaginal intercourse in more than 75% of attempts at the 100-mg dose.

Evaluation of Efficacy and Safety

Patients recorded the number of complete and partial intercourse encounters in a patient diary for 6 to 8 weeks. Success was defined as having penile erections rigid enough for vaginal penetration and of duration long enough to reach ejaculation. Any adverse events were recorded in the patient diary.

Results

Of the 714 men screened for the study, 58 patients (8%) were rejected for medical reasons. Of the remaining 656 men who were eligible for the study, 37 were lost to follow up (6%), and 98 (15%) elected not to participate because of their partner's concerns over treatment or reestablishment of sex activity. A total of 521 (93%) patients completed sildenafil treatment.

The distribution of etiologies was 68% organic, 8% psychogenic, and 24% a mixture of these. The most common associated risk factor was hypertension (39%), followed by hypogonadism (37%), and multiple medications (34%). Almost all patients (99%) who presented with hypogonadism had a concomitant medical condition. Other associated risk factors existed in less than 20% of the total population.

The median age of the entire population studied was 59 years. The median age of the responders was 58 (n = 427) and that of the nonresponders was 62 (n = 83). The age difference between responders and nonresponders was not significant ($P = .8$). Of the patients who reported success with sildenafil, the 50-mg dose proved efficacious in 66.2%; 4.7% found 25 mg efficacious, and 28.6% found 100 mg efficacious.

There was an overall 82% success rate with sildenafil use. Success at every attempt at intercourse occurred in 77% of patients. The Figure shows the success rate with sildenafil treatment for a number of risk factors and concomitant conditions. The success rates for patients with concomitant medical conditions ranged from 43% in patients who had previously undergone radical prostatectomy to 85% in hypogonadal patients with testosterone treatment, patients with neurological disease, and those who abused alcohol.

There was no significant difference ($P > .2$) between hypogonadal patients who were treated with testosterone before receiving sildenafil and those who were not treated.

The success rate was second highest in patients with hypertension (83%), following by those with tobacco abuse (80%), multiple medications (77%), and asymptomatic coronary artery disease (71%).

There was a higher percentage of failure in patients with multiple risk factors. In men who had both diabetes and hypertension (n = 43), for example, 35% failed with sildenafil treatment for ED.

Efficacy in the subgroup of patients with hypogonadism and known free testosterone levels (n = 44) was also assessed and compared with a control group of 44 men with normal free testosterone levels and similar concomitant risk factors. Men (n = 33) with slightly low testosterone levels (defined as 10.6 pg/mL) reported that 75% of attempts at intercourse were successful with sildenafil use. In the 16% (n = 7) of men with moderately low testosterone levels (8.1 pg/mL), sildenafil was somewhat efficacious, but less than 75% of intercourse attempts were successful. In the group of men (n = 4) in whom testosterone levels were severely low (7.4 pg/mL), none responded to sildenafil (ie, 0% successful attempts). By comparison, in the control group of 44 men with normal free testosterone levels, all attempts at intercourse (100%) were successful.

Eighteen percent of the total patient group were nonresponders (defined as failure in more than 75% of intercourse attempts) with sildenafil for the treatment of ED despite attempts to control associated risk factors.

Treatment-related adverse events (AEs) were generally mild to moderate. Flushing (20%) and headache (17%) were the most commonly reported AEs. Less than 2% of patients discontinued because of AEs.

Discussion

Overall Risk Factors

Few studies have assessed the efficacy of sildenafil in men with associated risk factors for ED in clinical trials (Feldman, 1998; Rendell et al, 1999), and few studies have examined the efficacy of sildenafil outside of clinical trials (Jarow et al, 1999; Marks et al, 1999; Virag, 1999).

Our results show high success rates with sildenafil treatment and concomitant treatment of a wide range of associated risk factors of ED in a multispecialty clinic setting. The success rate, defined as having penile erections rigid enough for vaginal penetration and of sufficient duration to reach ejaculation, was 82% overall compared with successful intercourse rates of 69% (Goldstein et al, 1998) and 65% (Padma-Nathan et al, 1998) in previous clinical studies of sildenafil. This also compares well with a 67% rate of successful intercourse (Virag, 1999) in a nonplacebo-controlled, clinical practice study in nonselected patients, a 78% response rate with a median 100-mg dose in a clinical practice study of men with chronic (more than 6 months) ED (McMahon, 2000), and a 65% efficacy rate in 267 men in a clinical practice setting of all patients treated with sildenafil within a 6-week period after its release (Jarow, 1999).

We hypothesize that the success rate with sildenafil treatment in our study is somewhat higher than in previous studies due to the attempted treatment modifications and control of risk factors. In our clinical practice, ED seems to be reversed in approximately 15% of cases when a change in treatment such as a change in heart disease medications (eg, beta-blockers) or antihypertensive agents (eg, thiazide diuretics), or modification of risk factors (such as smoking; Guay et al, 1998) is effected. Further
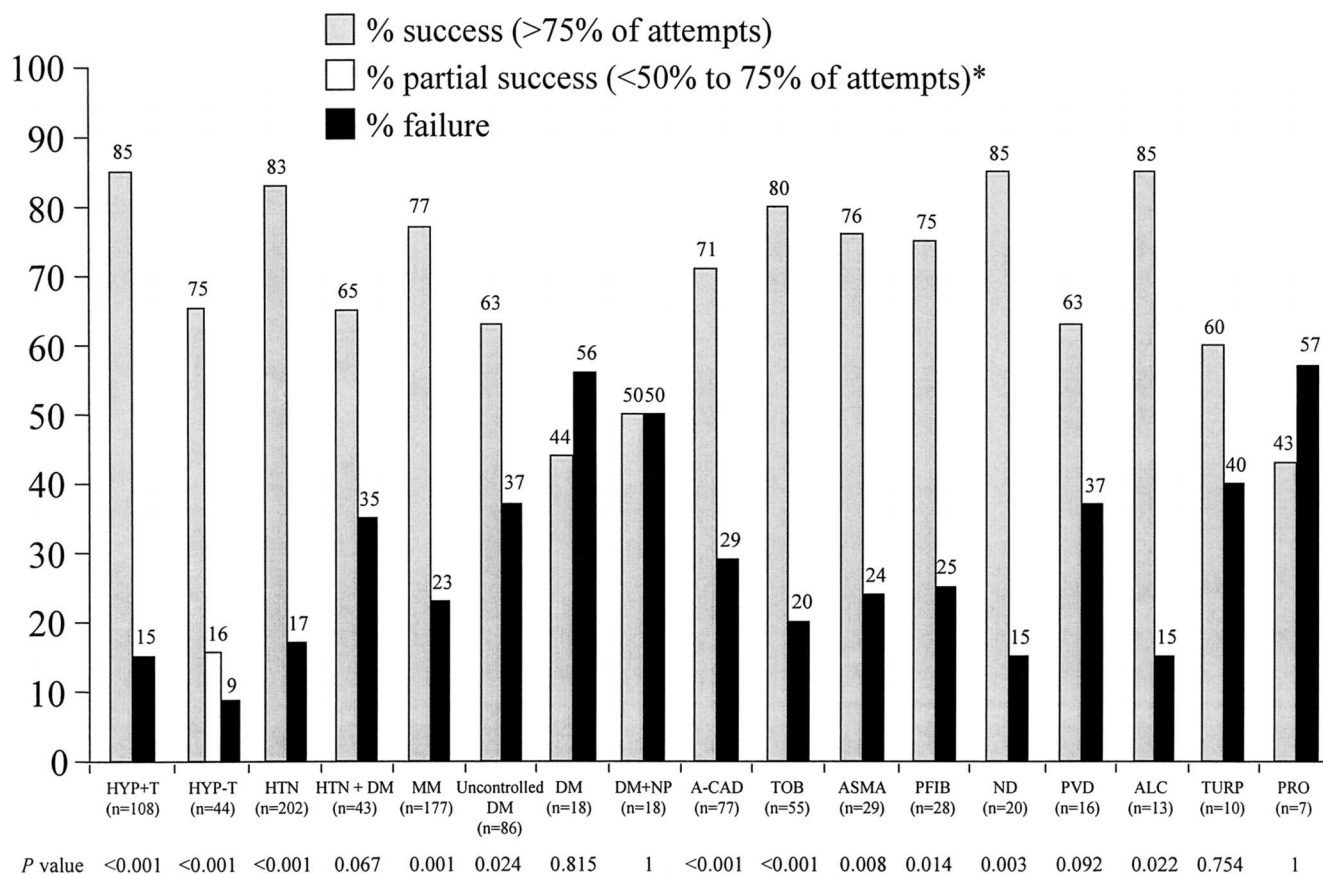
Success of sildenafil in patients with risk factors or concomitant conditions (percentages). Partial success was determined only in the HYP-T group. Proportions of successful versus unsuccessful patients for each condition were compared using binomial tests of independent proportions. Significant difference at $P \leq .05$. HYP+T indicates hypogonadism plus testosterone treatment; HYP-T, hypogonadism without testosterone treatment; HTN, hypertension; HTN+DM, hypertension plus diabetes mellitus; MM, multiple medications; DM, diabetes mellitus; DM+NP, diabetes mellitus plus neuropathy; A-CAD, asymptomatic coronary artery disease; TOB, tobacco abuse; ASMA, asthma; PFIB, penile fibrosis; ND, neurological disease; PVD, peripheral vascular disease; ALC, alcohol abuse; TURP, transurethral resection of the prostate; PRO, nerve-sparing prostatectomy. *Controlled; HbA1c <9%.

studies on the monitored control of risk factors and the use of sildenafil treatment for ED are warranted.

In the present study, a correlation existed in patients with more than one associated risk factor (ie, diabetes and neuropathy; hypertension and diabetes) and a lower rate of success with sildenafil treatment (13% to 18% less, respectively) than patients with only one associated risk factor.

Adverse Events

The incidence of AEs in our study was higher than in one of the initial published reports (Goldstein et al, 1998), but lower than in other later studies. For example, McMahon and colleagues (2000) noted facial flushing in 34% and headache in 23% of cases.

Hypogonadism

In our study, 33% of hypogonadal patients who received testosterone for 3 months found testosterone treatment alone efficacious for treatment of ED. Medical opinion is still divided about the efficacy of testosterone supplements in men with ED. Testosterone supplements (Arver et al, 1996) or raising endogenous testosterone (Guay et al, 1995) are frequently used for low or low-to-normal serum testosterone levels, but their efficacy on sexual function is not proven and has been labeled inappropriate as the sole source of erectile function restoration (Guay et al, 1995, 1999; Greiner and Weigel, 1996). In addition, previous studies have shown that testosterone as a treatment option does not positively affect sexual function in a significant proportion of patients (Korenman et al, 1990; Guay et al, 1995). However, during a secondary analysis of the patient population, we saw a slightly improved clinical response in men who were younger, who were healthier (Guay et al, 1995), and who received testosterone treatment.

Our results indicate that slightly low testosterone levels do not appear to be risk factors for ED, although we believe markedly low levels will cause difficulty in erectile response to sildenafil. In our clinical practice, we have

seen free testosterone levels of 5–6 pg/mL cause problems in erectile response when sildenafil is used (the normal range is 11–35 pg/mL for men aged 50 to 70). The levels in the group under study were in the 9–11 pg/mL range, and sildenafil is efficacious in this range.

Our study shows an increase in erectile function resulting from sildenafil treatment whether or not the patient received prior testosterone supplements. This indicates that the slightly lower than normal endogenous testosterone levels found were not contributing to ED and did not affect the response to sildenafil. Testosterone levels should be obtained routinely in order to find patients who are severely depleted, and to avoid overlooking patients with potential hypogonadism who may later develop signs and symptoms such as decreased energy, anemia, or osteoporosis.

Conclusion

The data presented corroborate earlier reports of the efficacy and safety of sildenafil when used as treatment in patients with ED (Goldstein et al, 1998; Padma-Nathan et al, 1998; Jarow et al, 1999; Marks et al, 1999, McMahon, 2000); furthermore, our data indicate that treatment with sildenafil while adequately controlling concomitant risk factors results in greater rates of efficacy than previously reported. In addition, whether or not hypogonadism is treated, response to sildenafil is similar unless the deficiency is severe (<7–8 pg/mL of free testosterone). Sildenafil treatment is efficacious and results in less than 2% treatment-related discontinuation due to intolerable side effects.

Acknowledgments

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