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REVIEW

Sildenafil use, sexual risk behavior, and risk for sexually transmitted diseases, including HIV infection

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KEYWORDS:
Sexual health;
Sexually transmitted diseases;
Gay/lesbian/bisexual/transgender persons.

ABSTRACT

PURPOSE: To determine the rates of sildenafil (Viagra) use among different populations, primarily among men who have sex with men, and to measure the association of sildenafil use with increased sexual risk behavior and sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection.

METHODS: The National Center for Biotechnology Information PubMed was searched using a variety of terms for relevant publications from January 1999 to July 2004. In addition, all scientific abstracts from national and international conferences on STDs from January 1999 to July 2004 were searched. Relevant journal articles and scientific abstracts presenting original data and meeting given criteria were included.

RESULTS: Fourteen studies met the inclusion criteria. Seven of the 11 studies in men who have sex with men showed sildenafil use rates >10% (range 3%–32%). Increased odds of unprotected anal sex with a partner of unknown or serodiscordant HIV status ranged from 2.0 to 5.7 times (mean = 3.9) for sildenafil users versus nonusers. The risk of sildenafil use and STD diagnosis among HIV-positive men who have sex with men was 1.92 ($P = 0.05$), and the odds of sildenafil use among those newly HIV infected was 2.5 (95% CI 1.1–4.1).

CONCLUSIONS: Most studies reported frequent sildenafil use in men who have sex with men, and several showed independent associations between use of the drug and sexual risk behavior, as well as an increased risk for STDs, including incident HIV infection. Although future research among more varied participants is needed, these results warrant a multi-faceted response to reduce the misuse of sildenafil and its consequences, particularly among men who have sex with men.

On March 27, 1998, the Food and Drug Administration (FDA) approved sildenafil (Viagra, Pfizer Inc., New York, NY) as the first oral pill to treat erectile dysfunction (ED). The drug quickly gained popularity, and it is estimated that since its approval over 16 million men worldwide have used the drug.[1] Recently, two additional drugs for the treatment of erectile dysfunction, tadalafil (Cialis, Lilly-ICOS Inc., Bothell, WA) and vardenafil (Levitra, GlaxoSmithKline Inc., Philadelphia, PA), have been approved. All three of these drugs work through the same mechanism: inhibition of the enzyme phosphodiesterase type 5, which leads to vasodilation and increased blood flow to the penis.

Although sildenafil was approved by the FDA for treatment of erectile dysfunction, recent information has arisen regarding use of the drug for the enhancement of sexual performance in men without a medical indication, as well as an association of its use with increased sexual risk behavior

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Table Select characteristics of studies on sildenafil use, sexual risk behavior, and STDs 1999–2004

Author, year (reference)	Study population	Exposure measure (sildenafil use)	Outcome measure	Measure of association
Publications				
Cachay et al, 2004[9]	Clinic-based convenience sample of 413 HIV-positive men in San Diego, median age 39	Prescriptions written 1 or more times: 7%	Insertive anal, vaginal, or oral sex without a condom	AOR = 3.0 (95% CI 1.0–8.9)
Hirshfield et al, 2004[8]	Convenience sample of 2916 MSM recruited through gay Web site, age range 18–60 years	Self-report use in past 6 months: 9%	Unprotected anal sex	AOR = 2.1 (95% CI 1.1–2.2)
Chu et al, 2003[5]	Community-based convenience sample of 837 MSM in SF, mean age 35	Self-report use ever: 32%	UAS with partner of unknown HIV status	AOR = 2.45 (95% CI 1.40–4.32)
Kim et al, 2002[6]	STD clinic-based convenience sample of 352 MSM in SF, median age 32	Self-report use in past 12 months: 31%	Among HIV-neg. respondents, UAS with partner of opposite or unknown HIV status	RR = 2.0 ($P = 0.05$)
			Among HIV-pos. respondents, diagnosis of STD (gonorrhea, chlamydia, or syphilis)	RR = 1.92 ($P = 0.05$)
Colfax et al, 2001[3]	Convenience sample of 295 MSM in SF who attended a circuit party in the past 12 month, median age 32	Self–report use in past 12 months at most recent circuit party: 14%	UAS with partner of opposite or unknown HIV status	AOR = 3.8 (95% CI 2.0–7.3)
Sherr et al, 2000[7]	Systematic sample of 677 MSM in London gyms*	Self-report use ever: 15%	Among HIV-neg. respondents, UAS with partner of serodiscordant HIV status while on sildenafil	RR = 5.7 ($P < 0.01$)
Aldridge and Measham, 1999[4]	Convenience sample of 519 persons at dance clubs in England, no age reported*	Self-report use ever: 3%	NA	NA
Abstracts				
Loeb et al, 2004[18]	HIV testing site-based convenience sample of 7145 repeat HIV testers in SF, no age reported*	Self-report use in past 12 months: 6%	HIV seroconversion	AOR = 2.5 (95% CI 1.1–4.1)
Mansergh et al, 2004[15]	Community-based convenience sample of 388 MSM in SF, no age reported*	Self-report use during most recent UAS: 6%	Unprotected insertive anal sex	AOR = 6.51 (95% CI 2.46–17.24)
Mitchell et al, 2004[13]	STD clinic-based convenience sample of 1263 MSM in SF, median age 36	Self-report use in past 4 weeks: 19%	Methamphetamine use in past 4 weeks	RR = 3.5 (95% CI 2.9–4.4)
Wong et al., 2004[17]	STD clinic-based convenience sample of 1225 MSM in SF, median age 36	Self-report sildenafil use with methamphetamines in past 4 weeks: 9%	Diagnosis of early syphilis	AOR = 6.2 (95% CI 2.6–14.9)
Brewer et al, 2004[14]	Systematic sample of 311 MSM in Seattle, no age reported*	Self-report use ever: 25%	UAS with HIV-pos. or unknown status partner	OR = 4.4 (95% CI 1.7–11.3)

Table Select characteristics of studies on sildenafil use, sexual risk behavior, and STDs 1999–2004 Continued

Author, year (reference)	Study population	Exposure measure (sildenafil use)	Outcome measure	Measure of association
Chiliade et al, 2004[12]	Gay men's clinic-based convenience sample of 700 MSM in Baltimore, no age reported*	Unknown	High-risk behavior for exposure to HIV†	AOR = 11.90 (P = 0.02)
Purcell et al, 2002[16]	Convenience sample of 1168 HIV-pos. MSM in SF and NYC, median age 41	Self-report use current: 12%	Unprotected oral insertive sex	OR 1.89 (95% CI 1.16–3.08)

AOR = adjusted odds ratio in multivariate analysis; BOR = bivariate odds ratio; MSM = men who have sex with men; NYC = New York City; RR = risk ratio; SF = San Francisco; UAS = unprotected anal sex.

*No age reported

†High-risk behavior defined as history within the last year of unprotected anal or vaginal sex, anal sex with more than one partner, intravenous drug use, sex with an HIV-positive partner, sex with an intravenous drug using partner, diagnosis of a sexually transmitted infection, and sex in exchange for drugs or money.

and sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) infection. This article reviews the current information regarding the prevalence of sildenafil use and its association with STDs, including HIV infection, focusing on studies from 1999 to the present. We then discuss the implications of these findings, as well as what possible actions should be taken to confront this public health issue.

Methods

To begin our review, we searched for available articles in the National Center for Biotechnology Information PubMed[2] using a variety of terms to maximize article return, including "Viagra and use," "Viagra and human immunodeficiency virus," and "Viagra and sexually transmitted disease." Similar searches were done using the terms Cialis and Levitra, as well as with generic drug terminology and abbreviated terms (sildenafil, tadalafil, vardenafil, HIV, STD). The search was limited to articles based on original data and written in the English language. To uncover additional articles, we searched PubMed using the last name of authors from pertinent articles, and we searched bibliographies of relevant papers for additional articles. In addition, all scientific abstracts from United States and international STD conferences from January 1999 to the July 2004 were reviewed. Of the relevant scientific abstracts found, we attempted to find original journal articles by the same authors publishing the data presented in the abstracts. Finally, we contacted researchers in the field of STD and HIV prevention, as well as the authors of pertinent scientific abstracts, to examine our compiled bibliography in attempts to find any missing relevant articles. The funding organization, the City and County of San Francisco, Calif, had no involvement in the design of the study, nor in the collection, analysis, and interpretation of the data.

Relevant journal articles and scientific abstracts presenting original data that met at least one of the following three criteria were included in our review: research on the prevalence of the use of sildenafil for enhancement of sexual performance among men without a medical indication; studies on the association between sildenafil use and sexual risk behavior, such as unprotected anal sex with a partner of unknown HIV status; and research focusing on the association between sildenafil use and STDs, including HIV infection.

Results

Our initial search of PubMed returned 1543 articles for "Viagra and use," 38 articles for "Viagra and HIV," and 4 articles for "Viagra and STD." Similar searches using the other ED treatment drugs returned 18 articles for "Cialis and use," 88 articles for "Levitra and use," 1 identical article for both "Cialis and HIV" and "Levitra and HIV," and no articles for both "Cialis and STD" and "Levitra and STD." Numerous duplicates were found among the various search terms. Of these, 7 publications[3-9] met our inclusion criteria. Of note, one article was excluded[10] because it presented similar data from an identical study population already indicated.[3] Another article[11] was excluded from review because it was an ecological study and presented no definitive data or conclusion. In addition, 7 scientific abstracts[12-18] met the inclusion criteria. All the relevant research focused on sildenafil use rather than either tadalafil or vardenafil use. Eight of the 14 studies (57%) sampled participants from San Francisco, Calif.[3,5,6,13,15-18] The Table provides a T1 select summary of the 14 reports.

The 14 studies showed that sildenafil use varied by population, time, and location. Prevalence of sildenafil use ranged from 3% use ever among men and women attending dance

clubs in England in 1999[4], to 32% use ever among men who have sex with men in San Francisco, Calif from 2000–2001.[5] Eleven of the 14 studies focused more specifically on sildenafil use among men who have sex with men,[3,5-8,12-17] and 7 of them found >10% of men who have sex with men had used sildenafil,[3,5-7,13,14,16] with particularly high levels (42%) among HIV-positive men who have sex with men.[5] One study found sildenafil use in men attending the San Francisco Municipal STD Clinic to be much more common among men who have sex with men than among heterosexual men (31% vs 7%, respectively).[6]

Eleven studies looked at the use of sildenafil and other recreational drugs,[3-8,13-17] including amphetamines, ecstasy, gamma-hydroxybutyrate (GHB), amyl-nitrates (poppers), and ketamine. The use of sildenafil and illicit substances were found in all 11 studies. Among MSM in the community in San Francisco, 36% of all sildenafil users combined its use with other drugs, including methamphetamines (23%), ecstasy (18%), poppers (15%), ketamine (11%), and GHB (8%).[5] A study among men who have sex with men that were seeking STD clinic services in San Francisco found sildenafil to be used concurrently with ecstasy (43%), methamphetamines (28%), and amyl nitrate (15%).[6] Among sildenafil users, 54% agreed that mixing sildenafil with other drugs enhanced the sexual experience.[6] Another study looking at a sample of men who have sex with men that were attending the San Francisco Municipal STD Clinic found sildenafil users more than three times as likely to have used methamphetamines in the past 4 weeks (risk ratio [RR] 3.5, 95% confidence interval [CI] 2.9–4.4).[13]

Four studies examined the source of sildenafil used by study participants, and all four found the majority (range 56% to 83%)[5,7] of sildenafil users reported obtaining the drug without a prescription.[4-7] Among a street-based sample of men who have sex with men that were in the community in San Francisco, 56% of sildenafil users did not obtain sildenafil from a physician, with 44% obtaining the drug from a friend, and 6% obtaining the drug on the Internet.[5] Similar statistics were found among men who have sex with men that were at the San Francisco Municipal STD Clinic.[6] Among men who have sex with men using sildenafil in London, 83% received the drug outside of the care of a healthcare provider.[7]

The studies reviewed focused on various outcome measures related to the use of sildenafil, with 11 of the studies using behavioral outcomes[3,5-9,12-16] and 3 of the studies using biological outcomes[6,17,18] (Note: Kim et al[6] used both behavioral and biological outcomes). Five studies[3,5-7,14] of men who have sex with men used unprotected anal sex with a partner of unknown or serodiscordant HIV-status, a high-risk behavior for HIV transmission, as a behavioral outcome measure. These studies found an increase in unprotected anal sex with a partner of unknown or serodiscordant HIV-status among sildenafil users, with users between twice as likely (RR = 2.0, $P = 0.05$)[6] to almost 6 times as likely (RR = 5.71, $P < 0.01$)[7] to engage in this risk behavior. One of the 5 studies looked specifically at sexual risk behavior while taking sildenafil and found HIV-negative men who have sex with men sildenafil users in London to be almost 6 times as likely as nonusers to engage in unprotected anal sex with a partner of serodiscordant HIV status (RR = 5.7, $P < 0.01$).[7] Two of the studies examined unprotected anal sex without specification of partner's HIV status as an outcome, and found sildenafil users to be 1.5 (adjusted odds ratio [AOR] = 1.5, 95% CI 1.1–2.2)[8] to over 6 times (AOR = 6.51, 95% CI 2.46–17.24)[15] more likely than nonusers to engage in this activity. Another study found HIV-positive men who used sildenafil to be almost twice as likely to engage in unprotected insertive oral sex with an HIV-negative partner (AOR = 1.89, 95% CI = 1.16–3.08) compared with nonusers.[16]

A study among HIV-positive men receiving care at a clinic in San Diego found those who had been written a sildenafil prescription were over 4 times as likely to have two or more partners during the past month, compared with those who had not received a prescription (AOR = 4.5, 95% CI 1.9–11.1).[9] Among men who have sex with men seeking public STD services in San Francisco, sildenafil users were found to have a higher average number of sex partners in the past 2 months compared with nonusers (5.4 partners vs 3.5 partners, $P < 0.01$). Fifty-two percent of sildenafil users agreed that the drug increases a person's ability to have more sex partners.[6]

Three of the studies focused specifically on biological outcomes in regard to sildenafil use.[6,17,18] At an STD clinic in San Francisco, among HIV-positive men who have sex with men who are sildenafil users were twice as likely (RR = 2.0, $P = 0.05$) to be diagnosed with an STD (gonorrhea, chlamydia, or syphilis) compared with nonusers. In multivariate analysis, sildenafil use was associated with having a new STD diagnosis after controlling for the number of recent sex partners.[6] Among a different sample of men who have sex with men, another study at the San Francisco Municipal STD Clinic found men using sildenafil and methamphetamines concomitantly to be more than 6 times as likely to be diagnosed with early syphilis (AOR = 6.2, 95% CI 2.6–14.9).[17] A study of 7145 repeat HIV testers at an HIV testing center in San Francisco found sildenafil users to be more than twice as likely to test positive for HIV infection (OR = 2.5, 95% CI 1.1–4.1).[18]

Discussion

In several geographical locations, the reviewed studies establish a substantial level of sildenafil use among a variety of samples of men who have sex with men. In these studies, sildenafil was often obtained without a prescription, and use of sildenafil was often combined with other recreational drugs, including methamphetamines and ecstasy. Numerous studies established an association between sildenafil use and increased sexual risk behavior, including unprotected anal

sex with a partner of unknown or serodiscordant HIV status, a major risk factor for HIV transmission.[19] In addition, studies found HIV-positive sildenafil users to be more likely to be diagnosed with an STD (gonorrhea, chlamydia, or syphilis),[6] and sildenafil users to be more than twice as likely to be diagnosed with HIV infection.[18] Although sildenafil itself does not cause these infections, the increased duration of erection, increased blood flow, and subsequent increased mucosal susceptibility may increase the risk of acquiring these infections if having sex with an infected partner.

Certain factors limited the findings of this review. The search strategy could have possibly overlooked relevant studies, although numerous steps were taken to prevent this oversight. The search was limited to English-only articles, thus possibly excluding studies from foreign, non-English speaking countries where sildenafil is available. The available research was limited to certain urban geographic areas, with the majority from the San Francisco Bay area, a finding that may limit generalizability. Several of the studies sampled from high-risk populations, such as patients at municipal STD clinics, and little data was available regarding use of sildenafil among heterosexual males. In addition, only 14 studies were available for review, 7 of which were abstracts, and only 3 of the 14 used biological outcomes.[6,17,18]

There were several limitations and strengths to the studies we identified. Most studies used a convenience sample of participants, and thus rates of sildenafil use may not be reflective of the entire population. Most of the studies reviewed were cross-sectional, so definitive causal inferences regarding sildenafil use and sexual risk behavior and STDs cannot be made. However, most of the studies used anonymous interviews or surveys, thus decreasing social desirability bias, limiting underreporting, and likely providing valid outcomes. Only one of the studies established an event-specific association between sildenafil use and increased sexual risk behavior,[7] as the others did not ascertain time of sildenafil use with regard to the specific behavioral outcome. The studies that measured biological outcomes used standard, FDA-cleared assays, thus limiting misclassification and providing more accurate measures of effect. Although this analysis does demonstrate a need for further research, the results of the reviewed studies support a strong association between sildenafil use and increased sexual risk behavior and increased risk for STDs, including HIV infection.

A community-based, random sample estimated the level of erectile dysfunction among American men to be 5% at age 40 and 15% at age 70.[20] A more recent study analyzing data from the National Health and Social Life Survey estimated the level of men with trouble maintaining or achieving an erection to be 9% between ages 30 and 39 years, and 11% between ages 40 and 49 years.[21] Another study in 1994 estimated the level of sexual dysfunction among men with a diagnosis of AIDS or an AIDS-related complex to be 53%.[22] However, those data were collected in 1990, before the advent of modern HIV therapy, and are likely not reflective of the study populations in the review.

Given these rates of erectile dysfunction, it is unlikely that sildenafil use rates as high as 32% in populations with a median age of 32 can be entirely attributed to the treatment of ED. This idea is reinforced by the data showing that many users obtained sildenafil from nonmedical sources, which increases its chance for misuse, and the frequent mixing of sildenafil with other recreational drugs. However, none of the studies reviewed asked sildenafil users why they were using the drug, including whether or not the drug was being taken for the treatment of ED. The review of the current data suggests numerous reasons for the use of sildenafil. These reasons include, but are not limited to the treatment of erectile dysfunction; counteracting the ED-producing effects of other drugs taken concordantly, including amphetamines and ecstasy; enhancement of sexual performance among men without a medical indication, including increased duration of erection, decreased refractory period, and the ability to have more partners in a short period of time; and facilitation of insertive anal intercourse in men who have sex with men, which requires a more rigid penis than oral or vaginal intercourse.[23]

A recent comprehensive study of sildenafil use among commercially insured adults in the United States from 1998–2002 found an 84% increase in usage rates of the drug by men and women from .8% in 1998 to 1.4% in 2002. The largest increase in sildenafil use was found among younger males aged 18–45 years, who had an increase in use of 312% from 1998 to 2002 ($P < 0.001$).[24] The study concluded that this large increase in use among a younger population suggested increased use of sildenafil for sexual enhancement or recreational use. However, this study solely focused on prescriptions for sildenafil among insured adults and thus is most likely an underestimation of use given the substantial number of sildenafil users, particularly among men who have sex with men, that are receiving the drug outside of prescription.

Methamphetamine has become a commonly used drug among many men who have sex with men, and 7 of the reviewed studies found increased levels of methamphetamine and sildenafil use among populations of men who have sex with men.[5,6,8,13-15,17] Methamphetamine use elevates motivation for sex but can also induce erectile dysfunction, as the drug may vasoconstrict peripheral blood vessels. To counteract this effect, some methamphetamine users mix its use with sildenafil.[23] The mixing of methamphetamines and sildenafil, as well as mixing with other recreational drugs, becomes particularly troublesome given the fact that the user is under the influence of these substances and thus may have impaired decision-making capabilities with regard to sexual risk behavior and the prevention of STDs, including HIV infection. Two studies found sildenafil use combined with amyl-nitrates (poppers).[5,6] Use of these two substances simul-

taneously is contraindicated, as it can cause severe hypotension and cardiac complications.

In 2002, the Centers for Disease Control reported an increase in STDs in the United States, including chlamydia and syphilis.[25] San Francisco has experienced a recent syphilis epidemic among the gay community, with rates from 1998 to 2002 increasing from 8 to 512 per 100 000 men who have sex with men. Cities such as Los Angeles, Seattle, Chicago, Miami, Boston, and New York City have experienced similar increases.[26] Furthermore, the Centers for Disease Control has reported a 17% increase in the number of newly diagnosed HIV infections among men who have sex with men since 1999.[27] Although numerous factors have undoubtedly played a role in this increase in new STD and HIV cases, sildenafil, given the prevalence of use of the drug and its association with increased sexual risk behavior and STDs, may be a contributing factor, particularly among frequent users and men who have sex with men.

Our analysis of the current body of information, taken into account with its limitations, offers suggestions for future research regarding sildenafil use, sexual risk behavior, and STDs, including HIV infection. It is important that future studies ask participants why they are using sildenafil; in particular, are users taking sildenafil for the treatment of erectile dysfunction? This information is instrumental in helping to define the current patterns of usage and to determine whether or not sildenafil users are using the drug for its FDA-approved and intended purpose. More time-specific data are needed regarding high-risk sexual behavior concurrent with sildenafil use. Studies in a greater variety of geographical regions are needed to solidify the generalizability of the findings. In addition, prospective studies in multiple populations are needed to establish temporality of sildenafil use preceding risk behavior.

In 2001, President George W. Bush issued an executive order creating the President's Council on Bioethics, a group of 17 of the United States' leading scientists, doctors, ethicists, and other professionals. The purpose of the council was to keep the President and the nation aware of new scientific developments and to provide a forum for the evaluation of profound issues.[28] In a 2003 report on biotechnology, the President's Council on Bioethics stated, "Viagra, a remedy devised for male impotence, is increasingly used by the nonimpotent to enhance sexual performance".[29] This statement from a preeminent national bioethical council demonstrates the significance of sildenafil use for nonindicated purposes, and further validates this ongoing public health problem.

Focused action is needed to respond to this ongoing public health problem. Although the current evidence of association exists only for sildenafil, likely due to the relatively recent approval of tadalafil and vardenafil, the needed action should focus on all three phosphodiesterase inhibitors (PDIs), as the observed associations with sildenafil use most likely would occur with drugs of identical nature. The labeling for PDIs should be modified to warn users of an increased risk for STDs, including HIV infection. Educational programs, particularly among physicians, men who have sex with men, and methamphetamine users, should be implemented to increase awareness as to the use of these medications and their association with STDs, including HIV infection. In addition, sufficient evidence exists concerning their use outside of a prescription, and the trafficking of the drugs, that consideration should be given to scheduling this class of drugs as a controlled substance.[30] It is imperative that healthcare providers, educators, regulatory bodies, and manufacturers mount a multi-faceted response in order to abate this ongoing public health problem.

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