REPORTS

The Bolger Conference on PDE-5 Inhibition and HIV Risk: Implications for Health Policy and Prevention

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ABSTRACT

Introduction. Recent reports have linked the use of phosphodiesterase type 5 (PDE-5) inhibitors with increased rates of high-risk sexual behavior and HIV transmission in some individuals.

Aim. A National Institute of Mental Health (NIMH)-funded, multidisciplinary conference was convened to evaluate scientific research, clinical and ethical considerations, and public policy implications of this topic.

Main Outcome Measures. Published and unpublished findings on effects of PDE-5 inhibitors on sexual behavior; published guidelines and management recommendations.

Methods. Leading investigators in relevant disciplines (e.g., public health, epidemiology, medical ethics, urology, psychology) participated in a 2-day meeting, including representatives of government, scientific, and regulatory agencies (the Centers for Disease Control, Food and Drug Administration, NIMH, and the National Institute on Drug Abuse). Panelists provided critical reviews of substantive areas of research, followed by question and answer sessions on each topic. On the second day, working groups were convened to identify critical gaps and priorities in three major areas: (i) research and evaluation needs; (ii) prevention strategies and clinical management issues; and (iii) policy and prevention implications.

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Results. Research needs and priorities were categorized into four specific areas: (i) basic and clinical/laboratory research; (ii) epidemiology and risk factors; (iii) social-behavioral processes and interventions; and (iv) prevention/policy and educational needs. Identified gaps in the available data include populations at risk (e.g., risk among heterosexuals, risk profiles among subpopulations of men who have sex with men) and the specific role of PDE-5 inhibitors in HIV seroconversion. Specific areas of emphasis were the need for safer sex counseling, comprehensive sexually transmitted infection (STI) screening and follow-up when indicated, avoidance of potentially dangerous drug interactions, and potential benefits of testosterone replacement for HIV-positive men with decreased androgen and other symptoms of hypogonadism.

Conclusions. A conference was convened on the topic of PDE-5 inhibition and HIV risk. This "white paper" summarizes the findings of the conference and recommendations for future research. **Rosen RC, Catania JA, Ehrhardt AA, Burnett AL, Lue TF, McKenna K, Heiman JR, Schwarcz S, Ostrow DG, Hirshfield S, Purcell DW, Fisher WA, Stall R, Halkitis PN, Latini DM, Elford J, Laumann EO, Sonenstein FL, Greenblatt DJ, Kloner RA, Lee J, Malebranche D, Janssen E, Diaz R, Klausner JD, Caplan AL, Jackson G, Shabsigh R, Khalsa JH, and Stoff DM. The Bolger Conference on PDE-5 inhibition and HIV risk: Implications for health policy and prevention. J Sex Med 2006;3:960–975.**

Key Words. Phosphodiesterase Type 5 (PDE-5) Inhibitor; HIV/ AIDS; Sexual Risk Behavior

Background

Phosphodiesterase type 5 (PDE-5) inhibitors are selective and highly effective peripheral vasodilator drugs that have been available worldwide since the late 1990s for treatment of male erectile dysfunction (ED). Three agents in this class (sildenafil, tadalafil, vardenafil) are currently available and are in use by approximately 20–25 million men worldwide [1–5]. The drugs are typically prescribed by a primary care physician, urologist, or other medical specialist for the treatment of ED associated with a potentially wide array of organic and psychogenic etiologies, including pelvic surgery, spinal cord injury, diabetes, hypertension, and depression [6–10]. PDE-5 inhibitors are considered to be safe and effective, although specific cautions and contraindications (e.g., coadministration of nitrates) have been noted. In addition to their widespread use in ED treatment, PDE-5s have potential benefits in the treatment of pulmonary hypertension (sildenafil has recently been approved for this purpose), as well as the management of congestive heart failure and benign prostatic hypertrophy. The introduction of PDE-5 inhibitors has revolutionized the treatment of ED and has brought relief to many millions of men with this common, age-related condition.

Despite these benefits, recent reports highlight the potential misuse of PDE-5 inhibitors as "recreational drugs," often in association with drugs of abuse, such as methamphetamines, MDMA (known as "ecstacy"), cocaine, and other stimulant drugs [11–14]. This pattern of misuse appears increasingly prevalent among men who have sex with men (MSM), and is associated with the practice of unprotected oral or anal sex, sex with multiple partners, and a potential increase in HIV transmission rates [15,16]. Additional concerns focus on potentially dangerous pharmacologic interactions when PDE-5 inhibitors are used in conjunction with inhalant nitrates or "poppers," or with certain antiretroviral or pharmacology-altering drugs. The popularity of PDE-5 inhibitors among MSM could be due, in part, to the drugs' purported capacity to allow multiple sexual partners within short time periods. It has also been suggested that PDE-5 inhibitors may be used to counteract the deleterious effects of stimulant drugs on peripheral vasoconstrictor mechanisms, which may lead to ED. Other anecdotal reports have suggested that PDE-5 inhibitors increase sensation for the receptive partner in anal intercourse [15]. Whereas higher prevalence levels of HIV transmission in some PDE-5 users are likely due to higher rates of unprotected sex, it has also been proposed that physiological mechanisms, such as changes in mucosal susceptibility related to increased pelvic vasocongestion, may play a role [16,17]. Regardless of the mechanism of action, the association between PDE-5 inhibitor use and a higher prevalence level of HIV has been noted in recent surveys, with some exceptions, and in studies with opportunistic samples of gay and

Table 1 Survey studies of PDE-5 inhibitors and HIV risk

Author(s)	Study population	Major findings
Ostrow	Multicenter AIDS Cohort Study, 7,000 MSM from four cities	Increased use of PDE-5s combined with other drug use classes
Hirshfield et al.	On-line cross-sectional study of 5,652 MSM in the United States and Canada	HIV status and crystal meth use associated with UAI but PDE-5s not independent predictors of UAI
Catania et al.	Two community-based surveys of MSM in 1996 and 2003	Higher levels of high-risk sexual behavior among men who used both meth and Viagra
Purcell et al.	Cross-sectional survey of HIV+ men in New York City and San Francisco	Viagra not related to sexual risk when controlling for illicit drug use
Spindler et al. [38]	Cross-sectional random telephone survey of 1,976 MSM in San Francisco	High HIV prevalence and risk behavior in men using both Viagra and meth
Latini & Coon	Anonymous survey of 203 MSM at San Francisco street fair, in-depth interviews with 32 older MSM with ED	Older MSM using PDE-5s and reporting high risk sex were also recreational drug users
Halkitis	Longitudinal study of drug use and sexual behavior among 450 gay/bisexual men	PDE-5s used frequently in combination with club drugs
Elford	Annual surveys of gay men in central London gyms between 1999 and 2005	Increase from 15% to 39% in Viagra use, more than 80% use in combination with recreational drugs

ED = erectile dysfunction; MSM = men who have sex with men; PDE-5 = phosphodiesterase type 5; UAI = unprotected anal intercourse.

bisexual men in the United States and the United Kingdom (see Table 1). The generalizability of these survey data is uncertain. None of the studies to date has investigated recreational use of PDE-5 inhibitors among men in conventional heterosexual relationships. This is a significant gap in the research literature to date.

Another problematic issue is the incomplete understanding of factors that determine high-risk sexual behavior generally, including the specific role of alcohol and other abused drugs. Individual and contextual factors have been shown in several studies to influence sexual risk taking, although the pathways or processes by which these factors lead to high-risk behaviors are not fully understood. Numerous studies have shown that the use of recreational drugs mediates high-risk sexual behavior in certain individuals; however, it is unclear which individuals are most likely to be affected by which drugs, and in which situations. The role of PDE-5 inhibitors in this context is a topic of particular concern. Although certain individuals are at an increased risk for both recreational drug use and high-risk sexual behavior, the independent and interactive effects of these risk factors have not been adequately investigated. More specifically, does the recreational use of PDE-5 inhibitors increase the likelihood of risky sex, independent of the effects of other situational or subject factors? If there is evidence for this effect, does it occur in heterosexual as well as homosexual men?

From the perspective of clinical management, HIV-positive men frequently suffer from erectile difficulties related to systemic effects of the disease, such as hypogonadism [18,19], or indirect effects related to increased fatigue and depression. Sexual dysfunction may be a side effect related to the use of protease inhibitors, other antiretroviral drugs, and certain antidepressants [20–22]. For many of these men, PDE-5 inhibitors may be effective in restoring erectile capacity, with or without the addition of testosterone replacement therapy. On the other hand, additional risks may need to be taken into account due to alterations in drug metabolism associated with antiretroviral therapies, or the use of nitrates for medical or recreational purposes (i.e., poppers). Moreover, Fisher [23] has noted the potential risks associated with testosterone replacement in HIV-positive men in the absence of interventions to increase safe sex practices. Few guidelines have been developed for managing ED in HIV-positive men, and for the use of PDE-5 inhibitors in this specific population.

In summary, several factors have led to increased concerns about PDE-5 inhibitor use, with or without the use of other recreational drugs or medical treatments, in HIV-negative or HIV-positive men. These factors include: (i) the widespread availability and use of PDE-5 inhibitors; (ii) the limited information most PDE-5 users are given in regard to potential drug–drug interactions, and the need for safer sex; (iii) the association of PDE-5 inhibitor use among MSM respondents in the community, and perhaps other groups of respondents, with risky sexual behavior; (iv) the co-association of PDE-5 inhibitors and widespread use of recreational drugs, particularly methamphetamines and other stimulant drugs; and (v) the prescription of PDE-5 inhibitors for men who are receiving medical treatment for HIV-related symptoms, including ED. Each of these factors has

contributed to increased attention in the media and professional literature to this topic.

To assess the quality of evidence and implications for public health, a multidisciplinary conference was convened with support from federal agencies, including the National Institute of Mental Health (NIMH), the National Institute on Drug Abuse (NIDA), and the Centers for Disease Control and Prevention (CDC). The conference included state-of-the-art presentations from the perspectives of basic science, survey research, clinical pharmacology, and public health. A major goal of the conference was to critically evaluate the evidence of increased use of PDE-5 inhibitors by high-risk individuals, and the potential contribution of these agents, with or without concomitant use of illicit or recreational drugs, to high-risk sexual behavior in HIV-positive or HIV-negative men. A related goal was to critically evaluate the state of knowledge regarding pharmacologic effects of PDE-5 inhibition on sexual behavior generally, and the potential interactions with other prescription or nonprescription drugs. A third major area for consideration was the treatment of sexual dysfunction in men with HIV/AIDS, and the potential risks and benefits of PDE-5 use in this group. Clinical management guidelines were addressed. Finally, the conference provided an overview of the regulatory, ethical, and social policy aspects of PDE-5 inhibitor use in high-risk or HIV-positive individuals [23]. Potential initiatives for education and prevention, particularly those involving collaboration of industry, academia, and government, were considered.

The conference was held on September 27–28, 2005 at the Bolger Center in Potomac, MD. Presentations by 24 faculty from four countries (the United Kingdom, Canada, Brazil, the United States) assessed current data on the biologic, epidemiologic, behavioral, and clinical management aspects of the topic. The content and speakers were reviewed in advance by a steering committee (R. Rosen, J. Catania, R. Stall, D. Stoff, J. Khalsa, A. Ehrhardt, J. Heiman, D. Malebranche). More than 100 conference attendees represented the academic community, public health agencies, regulatory and research agencies (the Food and Drug Administration [FDA], the CDC, NIMH and NIDA), and the pharmaceutical industry. A full day of academic presentations and discussion was followed by a half-day of working group meetings designed to develop guidelines and suggestions in the areas of research needs and priorities, clinical management and patient safety, and policy and prevention implications. The program agenda and speakers are included in Appendix I. This report presents an overview of the conference, a summary of the key findings from each of the scientific sessions, and the proposals developed in the three working group sessions.

Neurobiological Mechanisms

Normal penile erection depends on nonadrenergic, noncholinergic (NANC) innervation of the pelvic nerve and relaxation of smooth muscles in the penile corpora [2,23]. In response to sexual stimulation, cavernous nerves and endothelial cells release nitric oxide (NO), which stimulates the formation of cyclic guanosine monophosphate (GMP), which in turn causes relaxation of the corporal smooth muscle tissue and vasodilation of the penile arterioles. Sildenafil, vardenafil, and tadalafil are selective inhibitors of cyclic GMP-specific PDE-5. By selectively inhibiting cyclic-GMP catabolism in cavernosal smooth muscle cells, the drugs restore the natural erectile response to sexual stimulation, but do not cause erection in the absence of sexual stimulation. The drugs are generally effective in treating ED associated with psychogenic and/or organic etiologies, provided that the peripheral nerves and vascular smooth muscle mechanisms are intact.

Some controversy exists concerning the central nervous system (CNS) effects of PDE-5 inhibitors, and potential changes in libido or other centrally mediated aspects of sexual behavior. Some researchers have proposed that PDE-5 inhibitors alter NO transmission in the brain, thereby causing central side effects and changes in aggressive or sexual behavior [24]. However, this hypothesis is not supported by animal studies, which have shown minimal effects of PDE-5 inhibitors on brain mechanisms or function. The potential for these drugs to cross the blood–brain barrier is uncertain, and recent studies have shown that expression of PDE-5 in the brain is restricted to Purkinje neurons in the cerebellum. There is no known role for these neurons in the control of sexual behavior or other aspects of emotion. Changes in behavior that have been reported in observational studies or clinical trials are more likely associated with changes in erectile function or other autonomic effects of the drugs. Increased libido, for example, may occur in some men as a secondary effect of their renewed ability to achieve or maintain erections sufficient for sexual performance.

Burnett and McKenna reviewed current data on vascular and smooth muscle effects of PDE-5 inhibitors, in addition to the neurophysiological mediation of erection and potential behavioral effects of these inhibitors. These presentations found little evidence to support the hypothesis that PDE-5 inhibitors alter sexual behavior through direct central effects of the drugs. Further research is needed in this area, although the studies to date do not support direct effects of PDE-5 inhibitors on sexual desire or other centrally mediated aspects of sexual behavior.

Surveys of Sexual Behavior

Recent survey studies have indicated an association between the use of PDE-5 inhibitors and high-risk sexual behavior in selected samples of gay and bisexual men (see Table 1). In each of these studies, PDE-5 inhibitor use was associated with multiple sexual partners, or increased rates of unprotected oral or anal sex. Some recent studies have similarly shown a positive association between PDE-5 inhibitor use and increased sexual risk [16]. However, the strength of this association varied considerably from one study to another, as did the use of alcohol or other recreational drugs. PDE-5 inhibitor use was also associated with age and demographic factors, seropositivity status, and the use of antiretroviral and other prescription drugs.

The relationship between drug use (including PDE-5s, other prescription medications, and recreational drugs, such as alcohol, marijuana, cocaine, and methamphetamines) and high-risk sexual behavior has been the subject of a growing number of survey studies. Although the study populations and data collection techniques differ somewhat, the results of this work show several patterns and consistencies [16].

The Multicenter AIDS Cohort Study has followed almost 7000 gay and bisexual men in Los Angeles, Pittsburgh, Chicago, and Baltimore/Washington, DC, since 1984 [25]. Between 2000–2001 and the present, the odds of PDE-5 use increased by 3%, and the odds of using PDE-5s in combination with antihypertensives increased by 13%, whereas other drug use classes and combinations were relatively stable. Preliminary evidence suggests that certain attitudinal and personality traits may predispose these men to recreational drug use, combining recreational drugs with PDE-5s, and risky sexual behaviors.

Rates of PDE-5 inhibitor use and unprotected sex were assessed in the recent Seropositive Urban Men's Intervention Trial [26,27]. In this study, 1168 HIV-positive gay and bisexual men in New York City and San Francisco were recruited to participate in a multisite randomized intervention trial. Investigators assessed alcohol and drug use patterns among participants, and the association between drug use and sexual risk behaviors. A complex pattern of findings is evident. In regard to prescription drug use, 12% of respondents used sildenafil; use was associated with older age, being "white" or "other" racial group, self-identifying as gay, having more education, having an AIDS diagnosis, and taking antiretroviral medications. Men who used sildenafil had more sexual partners, and were more likely to engage in risky sexual behavior with casual partners, than men who did not use PDE-5 inhibitors.

Almost 60% of participants had used an illicit drug in the past 90 days, with the most commonly used drugs including marijuana (42%), poppers (26%), cocaine (18%), and methamphetamine (10%). Sexual risk behavior was most common among men who were younger, gay-identified, had a higher income, and were more highly educated. In addition, there were marked differences in the risk profiles of HIV-positive, and HIV-negative men and men with an unknown serostatus. For example, methamphetamine use was associated with risky behavior with all casual partners, whereas poppers were associated with sexual risk only for men who were HIV-positive or who had an unknown serostatus, and ketamine use was associated with sexual risk only for casual partners who were HIV-negative.

Preliminary data from an online study of 5,652 MSM in the United States and Canada who reported on their most recent sexual encounter with new or casual partners were collected by Hirshfield and colleagues in 2004–2005 [28,29]. Multivariate analysis of unprotected anal intercourse (UAI) among men with one partner vs. men with multiple partners in that encounter indicated that, regardless of number of partners per encounter, being HIV-positive and using methamphetamine before sex were significantly associated with UAI; men with single partners were significantly more likely to be over the age of 40 years. Additionally, use of PDE-5 inhibitors before sex in the most recent encounter was not an independent predictor of UAI, although the PDE-5 inhibitor may play a role in enabling men to engage in sexual activity, particularly in the context of drug and alcohol use.

Comparative data from two community-based probability studies of MSM indicated a significant

increase in the use of methamphetamines between 1996 and 2003, and a higher associated rate of seropositivity among methamphetamine users [12,28]. Men who used both Viagra and methamphetamines, comprising 10% of the 2003 study population, had significantly higher levels of risky sexual behavior, multiple sexual partners, and a 43% greater probability of being HIV-positive compared to men who used either one or neither of these drugs. Catania et al. suggest that men who use both methamphetamines and PDE-5 inhibitors are less likely to fear infection; men who use only Viagra or other PDE-5 inhibitors are not more likely to engage in high-risk sexual behavior.

This pattern was repeated in a household probability sample of 1,976 MSM in San Francisco. This study found that serodiscordant UAI was reported by 62% of men who used Viagra with methamphetamines, and significantly fewer men who used Viagra reported only UAI [29]. In fact, a positive association with condom use was found in one recent study [30]. In this study including in-depth interviews of older gay/bisexual men in San Francisco, it was found that most MSMs currently using PDE-5 inhibitors did not report increases in high-risk sexual behavior; moreover, some men found that use of PDE-5 inhibitors had actually increased their ability to maintain an erection while wearing a condom. As in other studies, men reporting PDE-5 inhibitor use in the context of high-risk sexual behavior tended to report other high-risk behaviors, such as increased use of recreational or "party" drugs, such as methamphetamines, ecstasy, and alcohol. This pairing of PDE-5 inhibitors with "club drugs" was similarly observed in a large-scale, longitudinal study of drug use and sexual behavior among 450 gay and bisexual men [31]. The precise association of PDE-5 use with sexual risk depended on the individual's club drug of choice, and it was difficult to determine the relative contribution of the PDE-5s, because polydrug use is so prevalent among this population.

Finally, in an annual survey of MSM in central London gyms [32], it was found that Viagra use had increased from 15% to 39% between 1999 and 2005. More than 80% of Viagra users reported recreational drug use, and HIV-positive men were more likely to have used Viagra than other men; in 2005, 57% of HIV-positive men reported Viagra use in the past 12 months, compared to 40% of HIV-negative men. Viagra use was associated with both protected and unprotected sex in this group of men.

Despite the repeated association observed between PDE-5 inhibitor use and increased rates of unprotected sex in these studies, a number of design and methodological problems in this research were noted. In particular, respondents were limited to gay and bisexual men, primarily in large urban centers. The use of alcohol and other recreational drugs was significant in each of these samples, and may have confounded the effects of PDE-5 inhibitors to a substantial degree. Furthermore, the role of behavioral traits or personality factors, such as sensation seeking or risk taking, has received little attention in this research. Bancroft and Janssen and colleagues, for example, have shown that sexual risk taking is influenced in some individuals by underlying neurophysiological tendencies toward high levels of sexual excitation, in combination with inadequate sexual inhibition [33,34]. This model might account for the effects of stimulant drugs, such as methamphetamines, in increasing risky sexual behavior in such individuals. On the other hand, the effects of PDE-5 inhibitors in such individuals have not been studied to date.

Overall, these studies provide support for at least three major conclusions. First, PDE-5 inhibitor use appears to be increasing among specific subgroups of MSM. Second, the precise patterns of PDE-5 use may vary, depending on the individual's age, seropositivity status, number of partners per encounter, and use of recreational drugs. Third, where PDE-5 inhibitor use is associated with increased sexual risk behavior, the relationship appears to be mediated by the use of recreational drugs. In the absence of recreational drug use, and particularly methamphetamines, the role of PDE-5 inhibitor use as an independent predictor of high-risk sexual activity remains uncertain. Moreover, it is not known to what degree the individual difference characteristics of those who choose to use PDE-5 inhibitors together with recreational drugs, might interact with either of these drugs alone or in combination, and are likely thereby to increase risky sexual behavior.

Safety Concerns Related to the Use of PDE-5 Inhibitors

Given the frequent coadministration of PDE-5 inhibitors with other prescription and nonprescription drugs, safety concerns have been raised regarding potential drug–drug interactions. In the presentation by Greenblatt, drug interactions with PDE-5 inhibitors were addressed. Individuals with HIV infection commonly receive medications to

treat the underlying disorder (viral protease inhibitors, nonnucleoside reverse transcriptase inhibitors [NNRTIs], nucleoside analogs), as well as drugs to treat other coexisting diseases (bacterial or fungal infections, cardiovascular/lipid disorders, psychiatric disorders, etc.). If such patients are also receiving treatment for ED with PDE-5 inhibitors, the possibilities for drug interactions with ED treatments are numerous [18]. Not all potential interactions can be studied clinically, but in vitro models based on Cytochrome P450 (CYP) enzymology can be of great help in anticipating likely drug interactions and targeting resources for clinical studies. CYP3A isoforms are of critical importance in the context of drug interactions with ED treatments, because the PDE-5 inhibitors depend largely or entirely on CYP3A for clearance. Inhibitors of CYP3A will impair clearance of ED drugs, significantly increasing serum plasma levels (2–14×) over prolonged periods. All HIV protease inhibitors and NNRTIs are CYP3A inhibitors to some extent, with ritonavir being the most potent inhibitor by far. Understanding of mechanisms and consequences of CYP3A inhibition by HIV treatments and other drugs can be of substantial value in anticipating and preventing potentially important interactions with PDE-5 inhibitors.

Cardiovascular risks associated with PDE-5 inhibitor use were addressed by Robert Kloner, MD. The specific concern is that all three PDE-5 inhibitors have synergistic, vasodilatory effects when taken in conjunction with nitrates in any form, including nitroglycerine, sublingual nitrates, or inhaled nitrates ("poppers"). Organic nitrates increase the production of cyclic GMP, whereas PDE-5 inhibitors prevent the breakdown of cyclic GMP. Hence these two types of agents, when administered in a concomitant fashion, can lead to increases in cyclic GMP and in some patients cause marked unpredictable vasodilatation and hypotension. PDE-5 inhibitors are absolutely contraindicated in patients who take nitrates. If deemed medically necessary, use of nitrates may be considered for patients who develop angina if 24 hours have passed since taking sildenafil or vardenafil, or if 48 hours have passed after the last dose of tadalafil. Concomitant use of any PDE-5 inhibitor with a nonselective alpha blocker (e.g., terazosin [Hytrin] or doxazosin [Cardura]) may lead to symptomatic hypotension in some patients, and there are precautions for the use of PDE-5 inhibitors (but not contraindications) with nonselective alpha blockers.

When PDE-5 inhibitors are administered with other antihypertensive medications, such as beta blockers, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, there are usually either no effects or small additive falls in blood pressure. Several studies suggested that patients taking multiple concomitant antihypertensives may be safely treated for ED with PDE-5 inhibitors. Numerous analyses have demonstrated that rates of myocardial infarction and death are not increased in men taking PDE-5 inhibitors compared to those taking placebo or compared to rates expected for age-matched populations. PDE-5 inhibitors administered prior to exercise stress testing in patients with known coronary artery disease did not worsen exercise tolerance, and did not exacerbate angina or ischemia compared to placebo. The PDE-5 inhibitors are safe in most stable cardiovascular patients as outlined in the recent Princeton II Consensus Guidelines [7,8]. These guidelines were recommended for use in individuals with a history of cardiovascular disease, including hypertension, myocardial infarction, angina, and heart failure.

Erectile Dysfunction in HIV-Positive Men

Sexual dysfunction, including complaints of loss of sexual desire (libido) and ED, are commonly reported by HIV-positive men. Loss of sexual function in these individuals has been associated with hypogonadism, depression, and other medical or psychologic sequellae [18]. Protease inhibitors, other antiretrovirals, and select antidepressants have also been associated with ED. Comorbid conditions, such as hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and peripheral vascular disease, may also contribute to the ED prevalence among HIV-positive men either directly or as a side effect of antiretroviral therapy [21,35]. Current treatment approaches include management of underlying medical and psychologic conditions, and testosterone replacement therapy for men with documented hypogonadism, with or without concomitant use of PDE-5 inhibitors for restoration of erectile function. (For a comprehensive recent review of hypogonadism effects in HIV/AIDS and the role of androgen replacement therapy, see [18].) Although to date there are no controlled trials of PDE-5 inhibitor use in the treatment of HIV-related ED, clinical reports indicate that the drugs may be of significant benefit in this context. However, the dosing and potential adverse effects related to drug–drug

interactions need to be carefully evaluated on a case-by-case basis.

Although in North America PDE-5 inhibitors should only be obtained with a prescription from a healthcare provider, small studies have suggested that MSM obtain these drugs from nonlegitimate sources (e.g., Internet pharmacies, "rave" parties). This brings into question the perceived accessibility to sexual health care by MSM and HIV-positive men.

Several presentations addressed the clinical management of sexual dysfunction problems in HIV-positive individuals, and specific benefits and risks of PDE-5 inhibitors in this population. In particular, speakers emphasized a need for thorough medical and psychosocial evaluation, assessment of the effects of concomitant drugs or diseases, and safety considerations related to the use of PDE-5 inhibitors. Special emphasis was placed on the need for counseling and education and prevention opportunities regarding safer sex practices, potential risks of recreational drug use, and drug–drug interactions [36,37]. This is an area in strong need of further attention. Sexually transmitted infection (STI) screening, in particular, is recommended for HIV-positive men with multiple sexual partners. With these considerations in mind, the panel observed that PDE-5 inhibitors can play a valuable role in the clinical management of sexual problems in HIV-positive men. The lack of scientific literature on erectile dysfunction and/or treatment in MSM was striking. More studies are needed of the outcomes associated with ED management in this population.

Societal Implications and Responsibilities

Several presentations addressed the societal implications of PDE-5 inhibitor use in high-risk sexual situations. To the extent that evidence suggests an association between PDE-5 inhibitor use and risky sexual behavior, where does the responsibility lie for addressing this issue? Faculty addressed the role of the pharmaceutical industry, potential effects of direct-to-consumer advertising on the widespread use of PDE-5 inhibitors, drug-labeling and FDA guidelines, bioethics and issues of individual rights and responsibilities, and the potential role of public health agencies and individuals. Although arguments were presented for increased governmental or regulatory control of prescribed PDE-5 inhibitor use, counterarguments were presented by several panelists. Daniel Shames, MD, Director of the Division of Reproductive and Urologic Products at the FDA, described regulatory policy and procedures in this regard and stated that he believed that the current labeling was appropriate. Other panelists noted the lack of sufficient evidence to support changes in drug labeling, in addition to the potential restriction of access to PDE-5 inhibitors in individuals with legitimate medical needs for the drugs. In the past 2 years, manufacturers have made voluntary changes in labeling, highlighting that this class of drugs does not protect against STIs and that precautions against STIs should be taken. Participants noted the considerable medical and psychologic benefits of PDE-5 inhibitors for many such individuals, and potential medical and ethical concerns associated with restricting access to the drugs. The need for increased education among professionals and the public regarding potential risks associated with recreational use of PDE-5 inhibitors was noted, and collaborative initiatives for the prevention of high-risk sexual behavior were strongly emphasized.

Working Group Summaries

Following the first-day presentations and panel discussions, a second half-day was devoted to three working group sessions on the topics of: (i) research needs and priorities; (ii) clinical management guidelines; and (iii) policy and prevention. Working groups consisted of approximately 30 participants per group, and included representatives from government, academia, health agencies and services, and the pharmaceutical industry. Each working group was charged with the task of developing an agenda for change, and proposals and guidelines in each of the three areas of focus. Each working group was moderated by two members of the conference faculty and steering committee. The suggestions of the working groups are summarized as follows:

Workshop 1

Research Needs and Priorities

Research needs and priorities in the area of PDE-5 inhibitor effects on sexual behavior were divided into four major areas: (i) basic and clinical/laboratory research; (ii) epidemiology; (iii) social-behavioral research; and (iv) policy implications and intervention needs.

The area of *basic research* encompassed both human and animal studies. Specific topics in this area included:

- animal models of the effect of PDE-5 inhibitors and other drugs (e.g., methamphetamines, cocaine, alcohol, steroids), and their effects on behavior and the cardiovascular system, including the penile arteries;
- the effects of PDE-5 inhibitors on the CNS;
- the effects of acute PDE-5 inhibitor use on cardiovascular syndromes;
- pharmacokinetics, drug interactions;
- possible facilitation effects of PDE-5 inhibitors on the biology of STI and HIV transmission;
- changes in viral load related to multiple ejaculations.

Questions related to *epidemiology* were both qualitative and quantitative in nature, and included:

- studies, both longitudinal and cross-sectional, to examine the role of PDE-5 inhibitors on the risk of new STIs and HIV infections;
- the possibility that PDE-5 inhibitors may play a positive role in reducing high-risk sexual behavior among some men;
- the underlying physical and behavioral mechanisms that relate drug use and sexual risk, emphasizing episode-specific data;
- methodological issues that need to be taken into account in data analysis, including clustering effects, sampling issues, recreational vs. treatment-related use, population (e.g., teens, young adult, all adults), and case–control studies;
- the prevalence of other forms of treatment for ED (e.g., penile injection therapy) and their relationship to sexual risk taking;
- the prevalence and impact of polypharmacy, including the use of steroids and recreational drugs, especially methamphetamine use; and
- partner characteristics and the use of polypharmacy and PDE-5 inhibitors.

In the area of *social-behavior research*, the group recommended work on such topics as:

- the direct positive and negative effects of PDE-5 inhibitors on risky behavior decision making in controlled laboratory studies, using random assignment of subjects;
- motivations for the use of PDE-5 inhibitors;
- better characterization of the populations that use PDE-5 inhibitors alone or in combination with other drugs;
- context of PDE-5 inhibitor use;
- social factors, including norms, networks, and dyads, that lead to PDE-5 inhibitor use;
- the impact of PDE-5 inhibitors on the quality of the sexual experience, and on mental health factors, and the impact of mental health on the use of PDE-5 inhibitors; and
- how men perceive penile function/dysfunction and how this may be changing with the introduction of PDE-5 inhibitors, and the effects of industry marketing and promotion.

On the topic of proposals related to *prevention and policy*, the group suggested research that would address

- greater clarity on the focus of prevention;
- physician-based studies related to knowledge of PDE-5 inhibitors and drug interactions, assessment and ongoing treatment, and counseling;
- patient–physician interactions around the area of sexual health;
- ethical "dilemmas" associated with the prescription of PDE-5 inhibitors to patients at high risk (e.g., those with HIV and other STIs);
- ethical responses regarding promotion and advertising on the part of the pharmaceutical industry;
- the "black market" for PDE-5 inhibitors, including national and international policy and regulations
- unregulated production of PDE-5 inhibitors—who produces the drugs and where;
- the effectiveness of government regulations in preventing the unregulated use of PDE-5 inhibitors;
- public knowledge of PDE-5 inhibitors, including the sources and quality of information about the drug;
- the relative effects of different modes of intervention to increase sexual health and general health literacy; and
- factors in help-seeking behavior for sexual health

Working Group II

Clinical Management of PDE-5 Inhibitor Use in HIV-Positive Men

International consensus guidelines have been published for the medical and psychologic management of ED in the broad population of men with this disorder [9]. Clinical guidelines also have been published for the specific management of cardiac risk associated with PDE-5 use in individuals with a history of cardiac disease or increased cardiac risk [7,8]. The working group on clinical management for this conference endorsed the overall applicability of these recent guidelines, with minor modification for use in HIV-positive persons. Additional areas of emphasis were: (i) the need for

safer sex counseling, comprehensive STI screening, and follow-up; (ii) avoidance of potentially dangerous drug interactions; and (iii) potential benefits of testosterone replacement for HIV-positive men with decreased androgen and other symptoms of hypogonadism. In assessing intervention needs of HIV-positive men and their partners seeking treatment for sexual dysfunction, the following HIV-specific and nonspecific management issues were considered.

HIV-Specific Concerns and Management Considerations

- Risk stratification
  - — Condom use (safer sex)
  - — Partner risk (partner counseling and referral services through health department)
  - — Medication and recreational drug use (see below)
  - — Substance use and dependency assessment

Stratification of Patients

- High medical and behavioral risks—refer to specialized HIV care center or provider
- Low risk—managed by primary care

Labs

- Fasting blood glucose
- Fasting lipid profile (total cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins)
- Thyroid function tests (thyroid-stimulating hormone, free T4, T3 levels)
- Liver function tests (liver enzymes, bilirubin, albumin)
- Morning testosterone (before 10 AM)
- STIs (pharyngeal, rectal, or urethral chlamydia and gonorrhea, Syphillis [RPR] and herpes simplex virus-type 2 antibody, hepatitis A and B serologies)

HIV-Specific Physical Exam

- Gynecomastia (from anabolic steroid use, hypogonadism, hyperprolactinemia)
- Signs of hypogonadism (testicular atrophy, tumor)
- Signs of STIs (sores, chancres, urethral or rectal discharge, condylomata)

Drugs Needing Dosage Adjustment in PDE-5 Users

Protease inhibitors (especially Ritonovir—increases PDE-5 inhibitor levels in blood)

- Ketoconazole
- Erythromycin
- Clarithromycin
- Rifampin/Rifabutin (decreases PDE-5 inhibitor levels in blood)

Drugs: Contraindications

- Nitrate, nitrite (oral and sublingual)
- Poppers (recreational nitrates)

Use of Recreational Drugs

Physicians should always enquire about use of these substances, particularly in HIV-positive individuals or men taking PDE-5 inhibitors.

- Poppers (amyl nitrate—lowers blood pressure especially in combination with PDE-5 inhibitors)
- Methamphetamine (cardiac)
- Cocaine (coronary constriction, elevated heart rate, and platelet thrombosis)
- Heroin
- Cannabis
- Alcohol
- Tobacco
- Anabolic steroids (testosterone, growth hormone)
- Ketamine (psychosis, "date rape" drug)
- Gammahydroxybutyrate GHB ("date rape" drug)
- Ecstasy (serotonergic agent in widespread use)

Precautions

- Type 1 and type 3 antiarrhythmics
- Nonselective alpha blockers

HIV-Specific Management

- Lifestyle modification (safer sex, exercise, recreational drugs, modifications of cardiovascular risk factors)
- Consider treatment of hypogonadism (clinical signs and testosterone level) prior to PDE-5 inhibitor
- Start with low dose of PDE-5 inhibitors if on protease inhibitor, particularly "boosted" regimens with Ritonovir

Indications for Specialist Referral

- Multidisciplinary care (HIV specialist, cardiologist, urologist, mental health professionals)
- Second- and third-line therapies can be considered
- Clinicians should bear in mind potential risks associated with penile injection therapy and surgical implants, in particular. These include urethral bleeding and increased risk of infection

with a penile implant, which is potentially a foreign body in immunocompromised patient; penile injections have increased risk of blood borne transmission. Follow-up
- ED status, treatment satisfaction
- Medical
- Psychosocial
- Lifestyle, safe sex
- Partner counseling and referral services
- Continued STI screening and follow-up.

Working Group III
Public Health and Prevention

Approximately 30 representatives of local and federal government agencies, academic institutions, and the pharmaceutical industry participated in this working group to suggest directions for public health and prevention related to PDE-5 inhibitor use and high-risk sexual behavior.

During initial discussion, the group determined that a primary focus should be placed on "WHAT can be accomplished, rather than WHO should do what." An emphasis on defining overall policy needs was seen as a necessary first step to inform the development of a comprehensive policy and prevention response. The group cautioned against generalizations or summary statements based on perceived responsibilities and roles of government, public health, or industry groups.

The group noted that it would be necessary to make these statements in the context of incomplete data, and that proposals were made in the spirit of what can be enacted in the short term, with a view to evolving policy as the evidence-base becomes firmer. Identified gaps in the available data include populations at risk (e.g., risk among heterosexuals, risk profiles among subpopulations of MSM) and the specific role of PDE-5 inhibitors in HIV seroconversion.

The overall suggestions of the working group included:

- capitalizing on the clinical setting to assess, counsel, and manage high-risk behavior that may be related to PDE-5 inhibitors and/or other drug use in high-risk settings;
- developing appropriate outreach methods and effective strategies to support safer sex behaviors in high-risk populations, and in venues that facilitate higher-risk sex, such as the Internet, sex clubs, bathhouses, bars, adult bookstores, and circuit parties;
- developing educational strategies that are based on social marketing and the promotion of social norms, which have shown merit in lowering rates of high-risk sexual activity related to the use of PDE-5 inhibitors and other drugs. These strategies should be defined and informed by a process of community input;
- expanding knowledge on the use of PDE-5 inhibitors and other drug use related to sexual risk behavior for other high-risk populations;
- supporting medical fellowships, faculty development, and public health expertise in sexual medicine, education, and prevention of high-risk sexual behavior;
- monitoring and evaluating current PDE-5 marketing and promotional efforts' impact on sexual risk behavior, STI, and HIV incidence;
- developing and expanding public health efforts in male reproductive health, as are now being undertaken in female reproductive health; and
- initiating external review of PDE-5 marketing and promotional efforts similar to external review required for HIV-prevention materials.

Summary and Conclusions

The Bolger Conference was convened to address the specific question of PDE-5 inhibitor effects on high-risk sexual behavior and potential consequence for HIV/AIDS transmission. Funding was provided by NIMH and NIDA. Additional support was provided by the CDC. Clinical, research, and policy articles were presented by 24 faculty from four countries (the United Kingdom, Canada, Brazil, the United States), who reviewed in detail the biologic, epidemiologic, behavioral, and clinical management aspects of the topic. This "white paper" summary includes a review of scientific research, both basic science and observational/clinical studies of PDE-5 inhibitor effects neurophysiologically, and in the context of emerging patterns of sexual behavior. In this regard, the co-association of PDE-5 inhibitor use with recreational or "party" drug use, was a major focus of attention. Based on the review of evidence and clinical considerations raised at the meeting, proposals were developed by three working groups (Research Priorities, Policy and Prevention Needs, and Clinical Management). An agenda for change and key proposals in each of these areas were noted by the three working groups and are summarized in this article. Overall, there was strong consensus on the need for additional short- and long-term studies of PDE-5 inhibitors, and possible links of PDE-5 inhibitor use to changes in sexual behavior and lifestyle factors.

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Appendix I

Conference Agenda and Presenters

Day 1	**Monday, September 26, 2005**
8:30–8:45	Welcome and Introduction: E. Stover Conference Overview: J. Catania, R. Rosen
8:45–9:30	Phosphodiesterase Type 5 (PDE-5) Inhibitors: A New Paradigm in Sexual Pharmacology Research and Treatment. Moderator: R. Rosen
	PDE-5 Inhibition: An Overview. Speaker: T. Lue
	Phosphodiesterase Type 5 Mechanisms and Role in Penile Erection. Speaker: A. Burnett
	The Central Nervous Control of Sexual Function: Is It Influenced by Phosphodiesterase Type 5 Inhibitors? Speaker: K. McKenna
	DISCUSSANT: J. Heiman
9:30–10:30	PDE-5 Inhibitor Use in High-Risk Populations: Is There Evidence of an Association? Moderator: J. Catania
	Viagra, Methamphetamine and HIV Risk: Results from a Probability Sample of MSM, San Francisco. Speaker: S. Schwarcz
	Sex, Drugs and Attitudes: Searching for the Common Underlying Causes of Risk Taking Among Gay/Bisexual Men in the Multicenter AIDS Cohort Study (MACS). Speaker: D. Ostrow

Appendix I Continued

	Does PDE-5 Inhibitor Use Predict Unprotected Sex Among Men Who Have Sex with Men? A Preliminary Report of a National Online Study. Speaker: S. Hirshfield
	Predictors of Viagra Use Among HIV Positive Gay and Bisexual Men in Two Urban Centers. Speaker: D. Purcell
	DISCUSSANT: W. Fisher
10:30–11:00	COFFEE BREAK
11:00–12:30	PDE-5 Inhibitor Use in High-Risk Populations. (Contd.) Moderator: R. Stall
	Patterns of Illicit Substance use, Viagra Use, and Sexual Behaviors Among Poly Club Drug Using Gay & Bisexual Men. Speaker: P. Halkitis
	Sildenafil Use and HIV Risk Among Older Gay/Bisexual Men: Research and Practice Implications from a Mixed Method Inquiry. Speaker: D. Latini
	Use of Viagra Among London Gay Men. Speaker: J. Elford
	Population Trends Among MSM in Methamphetamine, Viagra and High-Risk Behavior. Speaker: J. Catania
	DISCUSSANTS: F. Sonenstein and E. Laumann
12:30–1:30	**LUNCH** SPECIAL PRESENTATION: Maria Jose Delgado Fagundes (Brazil) PDE-5 Inhibitors and Direct-to-Consumer Advertising: The Brazilian Experience Discussant: Daniel Shames (U.S. FDA)
1:30–2:45	PDE-5 Use in HIV+ men and their Sexual Partners: Balancing Risks and Benefits. Moderator: D. Stoff Drug interactions with PDE-5 Inhibitors: Mechanisms and Prediction. Speaker: D. Greenblatt
	PDE-5 Inhibitors and Drug Interactions: Cardiac Safety Considerations. Speaker: R. Kloner
	ED Management in the HIV+ Patient: Benefits and Risks. Speaker: J. Lee
	DISCUSSANTS: D. Malebranche and J. Heiman
2:45–3:30	PDE-5 Inhibitors and High-Risk Sexual Behavior: Current Gaps in Research and Education? Moderator: J. Khalsa
	Theories and Definitions of Risky Sex: Challenges and New Developments. Speaker: E. Janssen
	First, Do No Harm: Ethical and Prevention Issues and PDE-5 Inhibitor Use in the Context of HIV Infection. Speaker: W. Fisher
	PDE-5 Inhibition and HIV Risk: Current Research Needs and Gaps. Speaker: R. Rosen
	DISCUSSANTS: R. Diaz and J. Catania
3:30–4:00	COFFEE BREAK
4:00–4:45	PDE-5 Inhibitors and High-Risk Sexual Behavior: Whose Responsibility Is It? Moderator: E. Stover
	Phosphodiesterase Type 5 Inhibitors (PDE-5s) and Public Health Policy. Speaker: J. Klausner
	PDE-5 Inhibitors and High-Risk Sexual Behavior: Whose Responsibility Is It? Speaker: D. Shames
	The Ethics of Recreational Use of PDE-5 Drugs: Whose Responsibility Is It? Speaker: A. Caplan
	PDE-5 Inhibition in the HIV+ Population: Clinical Perspectives. Speaker: G. Jackson
	DISCUSSANTS: A. Ehrhardt and D. Malebranche
5:00 PM	Conclusion

Commentary on Rosen RC, Catania JA, Ehrhardt AA et al. The Bolger Conference on PDE-5 inhibition and HIV risk: Implications for health policy and prevention

With the increased survival of HIV-infected men because of effective antiretroviral therapy, an important clinical question has emerged: what are the direct and indirect effects of PDE-5 inhibitors (PDE5i) in this group? Clinicians managing HIV-infected men who have sex with men (MSM) may plausibly believe that prescribing PDE5i will empower individuals by permitting adequate con-

dom usage on erect penises and thus reduce the onward HIV (and other STI) transmission. Unfortunately, the current data do not support this hypothesis. The Bolger conference report is a wide-ranging document, which attempts to bring together both expert opinion and the available, limited research data on PDE5i and sexual behavior in MSM. It should be noted that in Central and Western Europe, to say nothing of the developing world, the main mode of HIV acquisition is heterosexual.

The report quite correctly puts a large focus on the interaction of mind-altering illicit drugs used contemporaneously with PDE5i. In a specialist sexual dysfunction HIV unit in London, 75% (132/176) of those presenting with ED took recreational drugs on a regular basis while engaging in sex [1]. The practice is so common that it has a colloquial term—"chem-sex." It makes sense that many such drugs (e.g., methylamphetamine) would encourage PDE5i use to counter penile vasoconstriction. However, PDE5i use on its own may be an attractive option in young fit men in that it has been shown to result in supranormal penile rigidity [2]. Our anecdotal experience and a published report suggest that some men feel almost hypomanic when taking only PDE5i [3]. Recent animal and human studies appear to support this hypothesis [4–8].

An individual's sexual rights include whether or not to have sex in a consensual noncoercive relationship. He has an ethical duty to prevent, as far as possible, the spread of his HIV infection. Health care prescribing of PDE5i is thus the ideal scenario, because it can be incorporated into motivational health psychology to enhance a safer sex message, including condom use, which is singly the most effective method of reducing STIs.

However, PDE5i will continue to be obtained in nonmedical settings. Planning interventions to encourage safer sex in this scenario must clearly involve public health and sex education inputs, as well as a better understanding of relevant issues in MSM, such as the "drugs" culture, poor quality of life, low self-esteem, anxiety, and depression [9].

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Commentary on Rosen RC, Catania JA, Ehrhardt AA et al. The Bolger Conference on PDE-5 inhibition and HIV risk: Implications for health policy and prevention

In 1999, soon after the release of the first FDA-approved phosphodiesterase inhibitor in the United States, our group hosted a multidisciplinary continuing medical education (CME) seminar in New Jersey entitled "Treating Erectile Dysfunction in the HIV Positive Male." The focus of the meeting was on the medical, legal, and ethical aspects of treating this group of patients, with a special emphasis on the elderly population. During those earlier years of PDE-5 inhibitor availability, we had stated in our meeting conclusion that "although many more questions are raised than answered, this project was not aimed at dis-

covering 'The Right Answer,' but rather at examining objectively a difficult, real-time, clinical dilemma for which there has been little written or discussed to-date" [1]. The articles presented in this issue of the *Journal of Sexual Medicine* are important documents that address some of the earlier concerns and highlight a growing awareness of the issues relevant to the treatment of ED in the HIV-positive population. Although the Bolger Conference was mainly focused on one particular form of therapy (i.e., PDE-5 inhibitors) and HIV risk, the panels highlighted some of the broader issues affecting the patients, providers, partners, and the society as a whole. Worrisome trends in high-risk sexual behavior among those combining illicit drug use with PDE-5 inhibitors remind us all about the critical role of healthcare providers in continued patient education. On the brighter side, the notion that maintaining erections while wearing condoms is potentially facilitated by PDE-5 inhibitors indicates that a proactive approach to ED in the HIV-positive population may paradoxically result in "safer" sex because of therapy. The same may apply to addressing androgen deficiency in HIV-positive men.

Our role, although limited in the broader perspective of tackling the global HIV/AIDS problem, is exceedingly critical because what we do in treating erectile dysfunction goes beyond the typical doctor–patient relationship and involves a third party: the partner. Given the association of ED and aging, we are also likely to encounter a sizeable group of elderly patients with ED who may be at greater risk of becoming infected with HIV because of a variety of factors that include lack of education and information on HIV, greater freedom to practice unprotected sex without fear of pregnancy, and social stigma associated with HIV-positive status, leading to nondisclosure and unsafe practices [1]. Should we brush off any of this as "someone else's problem," we need only be reminded of these sobering facts: more than 65 million persons have been infected with HIV and more than 25 million have died of AIDS since the first report of AIDS in 1981; key prevention services are currently reaching less than 10% of those at risk; and 2005 was notable for more deaths and infections from HIV than ever before [2]. The problems of HIV/AIDS will not go away by being ignored, and the Bolger Conference has brought us one step closer to light. The meeting organizers and the authors of this report should be commended for their efforts.

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