Erectile Dysfunction Drug Use, Risk Behavior, and Sexually Transmitted Diseases

Tashina Robinson

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

University of Washington

2016

Committee:

Lisa E. Manhart

Stephen E. Hawes

Program authorized to offer degree:

Epidemiology

University of Washington

Abstract

Erectile Dysfunction Drug Use, Risk Behavior, and Sexually Transmitted Diseases

Tashina Robinson

Chair of the Supervisory Committee:
Dr. Lisa E. Manhart
Department of Epidemiology

Introduction: Erectile dysfunction is a widespread disorder in the United States, most commonly affecting men ages 40-70. Erectile dysfunction drugs (EDDs) are the standard treatment, but because of their ability to intensify sexual activity, they are also used recreationally. EDD use may therefore be associated with high risk behaviors that can lead to sexually transmitted diseases (STDs). We sought to examine this association and identify characteristics associated with EDD use among men seeking care for nongonococcal urethritis (NGU) in an urban STD clinic.

Methods: This cross-sectional analysis utilized baseline data from men attending the Public Health: Seattle & King County STD clinic who enrolled in the *Mycoplasma genitalium* Antibiotic Susceptibility and Treatment trial from January 2007 to July 2011. Men were eligible to participate if they were ≥ 16 years of age and were diagnosed with NGU (≥5 PMNs/HPF in a Gram stained urethral smear or visible urethral discharge). Patients completed a standard self-administered clinic electronic questionnaire collecting symptom, sexual behavior, and risk behavior data. Sociodemographic and clinical characteristics, STD diagnoses at enrollment, history of STD, and additional risk behavior data were abstracted from the clinic medical record. Study participants also completed a study specific computer-assisted self-interview collecting additional risk behavior data, including whether they had ever used any of 4 EDD drugs.

Results: A total of 597 sexually active men with NGU and complete data on EDD use were included in the analysis. Median age was 32 (IQR 25.6-39.8), 57.4% were White, 66.7% were men who had sex exclusively with women (MSW), 97% were HIV-negative, and the median number of sex partners in the prior 60 days was 2 (IQR: 1-3). The prevalence of EDD use was 18.8%, and prevalence was higher in men who had sex with male partners (MSM) than in MSW (28.1% versus 14.1%). Although condom use was not significantly associated with EDD use, men ≥ 45 years old were significantly more likely to report EDD use (adjusted prevalence ratio (APR): 7.42, 95% CI: 3.01-18.29, compared to 17-24), as were MSM (APR: 1.41, 1.01-1.95), ecstasy users (APR: 2.17, 1.60-2.94), men reporting ≥ $30,000 yearly income (APR: 1.70, 1.11-2.59, compared to < $10,000), or men with multiple sex partners in the past 60 days (APR: 2.10, 1.33-3.32) . However, STDs were not associated with either detection of prevalent STDs or history of STDs.

Conclusion: Among high risk men with NGU, EDD use was associated with older age and several sexual risk behaviors, but not unprotected sex. Despite these elevated risk behaviors, there was no significant association with increased risk of known sexually transmitted pathogens.

Introduction

Erectile dysfunction (ED), defined as the inability to get and keep an erection firm enough for sex,[1] is widespread in the United States with an estimated 18 million men affected.[2] Although ED can occur in sexually active men of any age, its primary cause is age-related decline in blood flow to the penis; therefore it most commonly affects men 40-70 years of age.[3,4] Four phosphodiesterase type 5 inhibitors have been approved by the FDA to treat ED: sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis), and avanafil (Stendra).[5] The oldest, Viagra, has been approved since 1998; the newest, Stendra, was approved in 2012.[4] These drugs are collectively known as erectile dysfunction drugs (EDDs) and work by increasing blood flow to the penis during sexual stimulation.[6] Although EDDs were approved to treat the medical condition of erectile dysfunction, they enhance sexual activity, are increasingly available on-line without a prescription, and therefore are also used recreationally.

EDD use is consistently more common in older than younger men. Among sexually active men attending Veterans Administration Hospital outpatient clinics, the odds of having 2 or more EDD prescriptions in the prior year were significantly lower for men < 40 years relative to older men, irrespective of sexual orientation. This relationship was particularly strong when comparing men ≥ 50 years of age to those < 40 (OR: 7.8, 95% CI: 3.1-19.8).[7] Similarly, men who have sex with men (MSM) > 25 years of age were more likely to report using Viagra for any reason (recreational or prescription) in the past 6 months than MSM ≤ 25 (34% versus 14%, $p < 0.001$),[8] and the odds of lifetime recreational use of EDDs were nearly 3 times higher in male undergraduates ≥ 23 years of age compared to those 18-22 years old.[9]

Although MSM and men who have sex with women (MSW) are equally likely to be prescribed EDDs,[7,10] MSM are more likely to use EDDs recreationally. Among male undergraduates, MSM had three-fold higher odds of lifetime recreational use of EDDs relative to MSW.[9] Although there are little empiric data on reasons for this higher recreational EDD use in MSM, their more frequent sexual activity as well as the ability of EDDs to counteract the sexual

side effects of stimulants such as methamphetamine, which are more commonly used by MSM, may partially explain it.[11]

EDD use has been associated with illicit drug use in general and methamphetamine, cocaine, and ecstasy use in particular.[5,7–10,12–16] EDD use has also been associated with risky sexual behaviors such as unprotected anal or vaginal sex and multiple sex partners.[3–8,10,12,14] Given this association with sexual risk behaviors, EDD use may also be related to the acquisition of sexually transmitted diseases (STDs), but data are sparse and inconsistent. Cross-sectional studies in undergraduate MSM and MSW[9] and men attending veterans hospitals demonstrated no association between reported EDD use and STDs.[7] Similarly, in a retrospective cohort study examining insurance claims in men over age 40, men using prescribed EDDs were more likely to have an STD before filling their first prescription, but there was no significant increase in STD rates after they began using EDDs.[17] Additionally, in a cross-sectional study of heterosexual "swinger" couples (couples who swap partners and/or engage in group sex) in the Netherlands, there was no association between EDD use in the past 6 months and STD diagnosis within 12 months.[18] In contrast, self-reported use of Viagra in the past year among HIV-positive MSM was associated with a higher prevalence of chlamydia, gonorrhea, and syphilis at enrollment (50 versus 26%; combined outcome p=0.05)[15] and having ever had an STD was predictive of Viagra use among illicit drug using men (OR: 2.17, 95% CI: 1.006-4.69).[12] In addition to the inconsistent results from these studies, most were conducted either in populations at low-risk for STDs (undergraduates[9] and older men enrolled in private insurance[17]), or in populations with high HIV prevalence and/or high HIV risk, including the Veterans Aging Cohort[7], men in care for HIV[10], or men attending HIV prevention clinics.[12] There are relatively little data about EDD use and STD risk among high-risk, predominantly HIV-negative men.

Men attending STD clinics with nongonococcal urethritis (NGU) represent a particularly high-risk group of men. NGU can be caused by several known sexually transmitted pathogens

including *C. trachomatis, M. genitalium, T. vaginalis*, and HSV.[19–21] Although up to half of cases are of unknown etiology,[22] some sexually transmitted infectious agent is likely the cause and men with NGU typically have higher levels of risk behavior than asymptomatic men. To expand our understanding of EDD use, we conducted analyses of this high risk group. We identified characteristics associated with EDD use and evaluated associations between use of EDDs and known sexually transmitted pathogens among men with NGU attending a public STD clinic.

Methods

Study Design and Data Sources

This was a secondary, cross-sectional analysis of baseline data from the *Mycoplasma genitalium* Antibiotic Susceptibility and Treatment (MEGA) study (ClinicalTrials.gov registration: NCT00358462). This randomized trial of the efficacy of two standard therapies for NGU enrolled men who were attending the Public Health Seattle-King County STD (PHSKC) clinic in Seattle, Washington from January 2007 to July 2011. Men were eligible to participate if they were ≥ 16 years of age and were diagnosed with NGU (>=5 polymorphonuclear leukocytes on a Gram-stained slide prepared from urethral exudates or a visible urethral discharge upon examination). Men who had taken antibiotics in the past month were excluded.

At clinic check-in, all PHSKC patients completed a standard self-administered clinic electronic questionnaire (kiosk) collecting symptom, sexual behavior, and risk behavior data. Study participants also completed a study specific computer-assisted self-interview (CASI) that collected additional risk behavior data and underwent a standard clinic exam. Sociodemographic and clinical characteristics, STD diagnoses, history of STD and additional risk behavior data were abstracted from the clinic medical record.

Measures

EDD use. EDD use was self-reported in the enrollment CASI. Participants were asked: "Have you ever used: sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra)?" (Stendra was not approved until 2012 and was therefore not included).

Sociodemographic Characteristics. Age was evaluated both in years (as a continuous variable) and categorically (17-24, 25-34, 35-44, and ≥ 45). Race was self-reported as White, Black, Asian, Pacific Islander, Native American, and Multi/other races and modeled as White and Non-White in multivariable analyses. Hispanic ethnicity was self-reported (Hispanic or Non-Hispanic) and assessed separately from race. Yearly income and highest education level were captured by the CASI. Income was categorized as < $10,000, $10,000-29,999, and ≥ $30,000 and education level was categorized as ≤ high school/GED and > high school.

Risk Behaviors. Lifetime drug use (ecstasy, methamphetamine, and cocaine) was captured in the CASI as were sexual behaviors in the past 60 days (number of sex partners and whether vaginal, oral, or anal sex occurred). Number of sex partners in the past 60 days was also categorized as 0, 1, 2, or ≥ 3 partners and assessed as a binary "yes/no multiple partners in the past 60 days" variable in multivariable analyses. Condom use during anal or vaginal sex in the past 60 days was captured in the medical record as "Always," "Sometimes," "Usually," or "Never" for those who engaged in either insertive anal or vaginal sex during that time period. Condom use was assessed as "consistent" (always) and "inconsistent" (less than always) in multivariable analyses. Sex of partners within the past 12 months was captured in the kiosk; men were categorized as MSM if they reported any male sex partners and as MSW if they reported exclusively female sex partners.

Sexually transmitted pathogens. Chlamydia trachomatis and *Neisseria gonorrhoeae* were detected by the APTIMA Combo 2 TMA assay and *Trichomonas vaginalis* was detected

using analyte specific reagents for the Aptima TMA assay (Hologic [formerly Gen-Probe], Inc. San Diego, CA). *M. genitalium* and *Ureaplasma urealyticum* biovar-2 (differentiated from *U. parvum*) were detected by in-house PCR assays at enrollment.[21,23] HIV status (history of HIV or diagnosis at enrollment using enzyme immunoassay or western blot), HSV-1 or HSV-2 genital herpes simplex virus infection (history of herpes or diagnosis at enrollment in serum using either an enzyme immunoassay or by direct culture of lesions), genital warts, and history of syphilis were captured in the medical record and coded as positive/negative.

An aggregate variable for "any STD at enrollment" was created and included detection of *C. trachomatis, T. vaginalis, M. genitalium*, or new diagnosis of HIV, or herpes. Given the inconsistent data regarding whether *U. urealyticum* biovar-2 is a pathogen, this organism was not included in the classification of the "any STD" variable. "Any STD at enrollment" was further categorized into "any bacterial STD at enrollment" (detection of *C. trachomatis*, *T. vaginalis*, or *M. genitalium*) and "any viral STD at enrollment" (new diagnosis of HIV or herpes).

An aggregate variable for "history of any STD" was created and included a prior diagnosis of chlamydia, gonorrhea, syphilis, HIV or herpes (history of trichomoniasis was not recorded). "History of any STD" was further categorized into "history of bacterial STD" (past diagnosis of chlamydia, gonorrhea, or syphilis) and "history of viral STD" (past diagnosis of HIV or herpes).

Analysis

In univariable analyses, we compared characteristics of men reporting and not reporting EDD use and of MSM and MSW, using Fisher's exact test for categorical variables and student's t-test for continuous variables to determine the statistical significance of differences.

A multivariable Poisson regression model with robust standard errors was utilized to identify factors independently associated with EDD use. Any characteristic that was associated with EDD use in univariable analysis at $p<0.10$ was evaluated for inclusion in the model. These

factors were entered into the model one at a time and retained if they were statistically significant at $p<0.05$, using a Wald test. Effect modification by age category and by sexual orientation was initially assessed through stratified analyses. In cases where prevalence ratios (PRs) differed appreciably between the strata, interaction terms between each characteristic and the potential effect modifier were evaluated in the model and retained if statistically significant at $p<0.05$ using Wald tests.

Similarly, to examine the association between EDD use and STDs, either STD detected at enrollment or reported history of prior diagnoses, additional multivariable Poisson regression models with robust standard errors were developed. Characteristics that were associated with both EDD use and with STDs were entered into the model and retained if they changed the prevalence ratio by ≥ 10%. Statistical significance was determined using Wald tests set at $\alpha=0.05$. In sub-analyses, the association of EDD use with *C. trachomatis, M. genitalium*, herpes, and HIV was examined individually, using the same methods described above.

Results

Of the 606 men included in the MEGA study, 2 participants did not have EDD use information, 4 were positive for *N. gonorrhoeae* at enrollment, and 3 had not had sex in the past year, leaving 597 for these analyses. The median age of participants was 32 (IQR: 25.6-39.8); 57.4% were White, 66.7% were MSW, 97% were HIV negative and the median number of sex partners in the past 60 days was 2 (IQR: 1-3). Of the 597 men, 112 (18.8%) reported ever having used EDD. Among MSM, the prevalence of EDD use was 28.1%, whereas it was 14.1% among MSW.

Characteristics associated with EDD use

In univariable analyses, EDD users were older, more likely to be MSM and more often White ($p<0.001$ for all) (Table 1). They were also of higher socioeconomic status, as demonstrated by higher levels of education and income ($p<0.001$ for each), and more likely to have ever used methamphetamine ($p<0.001$) or ecstasy (0.001). Within the past 60 days, EDD users were also significantly more likely to have had ≥ 3 sex partners ($p<0.001$).

Comparing MSM to MSW, MSM were more likely than MSW to be White ($p<0.001$) and Hispanic ($p=0.011$), and to have a greater than high school education ($p<0.001$) and an income of ≥ $30,000 per year ($p<0.001$) (Table 2). They were also more likely to have ever used methamphetamine ($p=0.04$) or cocaine ($p=0.04$), but not ecstasy. Within the past 60 days, MSM reported more sex partners ($p<0.001$), and were more likely to report insertive anal or insertive oral sex than MSW ($p<0.001$ for both behaviors), as well as more consistent condom use ($p<0.001$).

In multivariable analyses, there was no significant effect modification when stratifying by sexual orientation. Although there were some minor differences in PRs in age category strata, no interaction terms with age were statistically significant. Therefore, aggregate rather than stratified multivariable analyses are presented.

Age, sexual orientation, ecstasy use, yearly income, and having multiple sex partners in the past 60 days were independently associated with EDD use in multivariable analyses. Increasing age was associated with stepwise increases in reported EDD use. After adjusting for sexual orientation, ecstasy use, yearly income, and multiple sex partners, men 25-34 were over twice as likely as men < 25 years of age to report EDD use (adjusted PR (APR) 2.63, 95% CI: 1.08-6.44) (Table 3). Similarly, men 35-44 were 5 times as likely (APR: 5.00, 95% CI: 2.06-12.17), and men ≥ 45 were over 7 times as likely (APR: 7.42, 95% CI: 3.01-18.29) to report EDD use relative to men aged 17-24. MSM were more likely than MSW to report EDD use (APR: 1.41, 95% CI: 1.01-1.95), as were men who had ever used ecstasy relative to those who had not (APR: 2.17, 95% CI: 1.60-2.94), and men with multiple sex partners in the past 60 days

relative to those with 0-1 sex partners (APR: 2.10, 95% CI: 1.33-3.32), adjusting for the other model characteristics. After similar adjustment, men with an annual income of ≥ $30,000 were more likely to report EDD use than men with incomes < $10,000 per year (APR: 1.70, 95% CI: 1.11-2.59), but there was no difference between men who earned $10,000-29,999 and men who earned less.

Association between EDD use and sexually transmitted pathogens

In univariable analyses, EDD users were somewhat less likely to have any STD (32.1% versus 40.0%, p=0.12) and specifically any bacterial STD pathogen detected at enrollment (30.4% versus 38.6%, p=0.10), but this was not statistically significant (Table 4). This inverse association was predominantly related to *M. genitalium* infection (8.1% versus 14.5%, p=0.09), and there were no other associations with additional bacterial STD pathogens.

Despite the absence of a significant association with prevalent bacterial STD pathogens, EDD users were more likely to report a history of any of the STDs examined. This was true both individually (p<0.05 for all but *C. trachomatis* (p=0.06)) and aggregated as “history of any STD” (67.3% versus 51.5%, p=0.003), “history of bacterial STD” (61.8% versus 46.5%, p=0.004), or “history of viral STD” (24.3% versus 12.8%, p=0.002).

In multivariable Poisson regression models, there was no significant association between EDD use and STDs . None of the potentially confounding characteristics that we evaluated appreciably changed the PRs for the association of any STD or any bacterial STD at enrollment and only crude PRs are presented. Adjustment did not change non-significant associations with prevalent *C. trachomatis* or *M. genitalium*, or with new diagnoses of HSV or HIV. Although history of any STD and history of any bacterial STD were associated with EDD use in univariable analyses, these relationships were no longer statistically significant after adjustment for age and further adjustment for multiple sex partners in the past 60 days made no

appreciable difference. Additionally, the significant association between EDD use and history of viral STD was no longer statistically significant after adjusting for age and sexual orientation.

Discussion

Nearly 20% of men with NGU attending a public STD clinic reported EDD use and age, sexual orientation, ecstasy use, yearly income, and having multiple sex partners in the past 60 days were independent risk factors for EDD use. The strongest risk factor was age, with a stepwise increase in reported EDD use as age increased, even in this relatively young population. Additionally, MSM, men who had ever used ecstasy, men with higher incomes, and men with multiple sex partners in the past 60 days were approximately 1.5–2 times as likely to report EDD use as men who did not report this. Despite this elevated risk behavior among men who had reported using EDDs, after adjustment for confounding factors there was no significant association between EDD use and STD diagnosis.

Overall, previous estimates of the prevalence of EDD use range from a low of 5% in undergraduate males to a high of 35% in a sample of MSM attending a sex resort.[7–10,13–17,24,25] Our estimate of 18.8% prevalence of EDD use among these predominantly heterosexual men with NGU under the age of 40 falls in the middle of this range. Within our sample, the prevalence of EDD use was 14.1% in MSW and 28.1% in MSM. Comparatively, among men seeking public health STD clinic services in San Francisco from 2000-2001, 7% of MSW and 31% of MSM reported Viagra use in the past year.[15] The higher prevalence in MSW that we observed may be due to how EDD use was defined in each study. The San Francisco study evaluated use in the past year while we evaluated lifetime use, and we would expect to see a higher prevalence of lifetime use. The higher prevalence in MSM observed in both settings is likely due to the more frequent recreational use of EDDs by MSM in general.[9] The comparable yearly and lifetime prevalences in MSM in San Francisco and Seattle likely indicate regional

variations in EDD use. Furthermore, since the San Francisco study was conducted shortly after the introduction of Viagra, there may be changing trends in usage and availability over time.

In this study population, MSM were more likely to use EDDs than were MSW, and MSM in our sample had higher levels of each risk behavior evaluated except for ecstasy use. Even though ecstasy use has been associated with sexual orientation in young populations (12-24),[26,27] our study sample was predominantly over the age of 25 and the absence of an association here suggests that the link between being MSM and ecstasy use may diminish over time. Although MSM and MSW are equally likely to be prescribed EDDs,[7,10] MSM have higher levels of sexual activity (more partners, higher rates of partner change, higher rates of unprotected sex)[28] and methamphetamine use,[11] both of which can be facilitated with EDDs, and this may partly explain their more frequent use. In a sample of undergraduates, MSM were 3 times more likely to recreationally use EDDs[9] and MSM had a prevalence of EDD use over 4 times higher than MSW in a cross-sectional sample of San Francisco STD clinic attendees.[15] In contrast, in a study of recreational EDD use among healthy young Brazilian men, there was no difference between MSW and men who were “not MSW.”[6] However, there were only 26 men in the sample who were not MSW, 20 of whom identified as homosexual or bisexual and 6 of whom did not disclose their sexual orientation (N=321) and these findings should be interpreted cautiously.

Although lower income is associated with drug use in general,[13] having a higher income was independently associated with EDD use in these men with NGU. However, since EDDs also serve a medical need and having a higher income is associated with treatment seeking behaviors,[29] a higher-earning man may be more likely to seek care for his erectile dysfunction. Furthermore, a man with more disposable income may have greater ability to purchase an EDD for recreational use.

Our observation that older age was independently associated with EDD use is consistent with previous literature overall. Multiple studies have linked older age to EDD use,[7–9] even

among men in their 20s and 30s. While older men ages 40-70 are most likely to have ED,[3] a 2013 Italian study found that nearly 26% of new ED cases in an outpatient clinic were men under 40 years of age,[3] suggesting an increase in ED in younger men. Conversely, a study of MSM attending a “sex resort” in 2004 did not observe an association between age and EDD use within the past 3 months.[25] However, this was likely due to the venue and reason for use. In populations where EDD use is primarily recreational, age may be a less important factor.

EDD use was independently associated with ecstasy use and this may be because it is believed to intensify the effects of ecstasy.[8] The two drugs may be purposefully used together to enhance a user’s experience. Moreover, users of other drugs may be more likely to try an EDD.[12] However, we did not observe any association between EDD use and cocaine in this population, nor did we observe a statistically significant association between EDD use and methamphetamine in multivariable analyses. This was unexpected, given that both cocaine and methamphetamine have similar erectile dysfunction effects and users of both drugs may experience problems getting and keeping an erection. The absence of an association between EDD use and cocaine use may be due to the sexual behaviors and attitudes associated with this drug. While both cocaine and methamphetamine are stimulants, methamphetamine is more strongly associated with increased sexual desire and sexual episodes. Among outpatients treated at a California drug abuse clinic, methamphetamine use was more strongly associated with a positive sexual relationship including an increased sex drive and likelihood of having sex; conversely, cocaine use was associated with negative outcomes, such an abnormally low sex drive and self-harm after sexual activity.[30] Therefore, cocaine users likely do not have a heightened interest in sexual activity, and may not seek drugs to enhance sexual experiences. Although methamphetamine has been associated with EDD use, it did not emerge as an independent risk factor in our study. This may be because the practice of mixing the two drugs occurs predominantly in the gay community.[14,31] The MSM group in our study consisted of both

gay men and bisexual men (26%), and this “mixing” of EDDs and methamphetamines may be less prevalent in bisexual men.

Having multiple partners in the past 60 days emerged as an independent risk factor for EDD use and this is generally consistent with the literature. EDD use has been associated with having more sex partners in the past 30 days, 60 days, and over a lifetime.[9,12,15] Only a single study observed no association with multiple sex partners: in a community-based sample of healthy young men using EDDs recreationally, those who had occasional partners in the past 6 months were not significantly more likely to use EDDs than those who had one stable partner.[6] This lack of association may be because a man with a stable partner has more opportunity for sex and, therefore, more need/desire to use an EDD than men with occasional partners.

Condom use was not associated with EDD use in these men with NGU. Previous research has generally indicated a link between unprotected sex and EDD use in both MSM and MSW.[7–9,14] However, in a study of young men using recreational EDDs in Brazil, there was no association between unprotected sex and EDD use. The authors of this study proposed that men who have problems retaining an erection when using a condom may use EDDs to counteract this.[6] This explanation is supported by observations in a sample of healthy young men where 26% reported difficulties keeping an erection with a condom and 71% of EDD users believed that EDDs could facilitate condom use.[32] Alternatively, men who use EDDs to enhance their sexual experience could be aware that they may engage in high risk sexual behaviors and use condoms more often. Finally, the absence of an association between condom use and EDDs may be due to social desirability bias. Condom use in our study was assessed through clinician-interview rather than by CASI. Patients may have falsely reported condom use to their clinician in an effort to appear responsible and/or to avoid further testing.

No significant association with STDs was found for EDD use after adjustment for confounding factors, including age, income, race, sexual orientation, and/or multiple sex partners. This is consistent with most other studies. For example, there was no association

between lifetime EDD use and lifetime STD diagnosis in undergraduate males[9] and there was no association with 6-month EDD use and STDs diagnosed within the past year in a study among swingers in the Netherlands, although this latter study also had very low power to detect STDs in men.[18] Additionally, no association between EDD use and STDs was observed in studies where EDD use was measured by prescription records; [7,17] however, men who obtain EDDs by prescription probably use them for medical reasons rather than to facilitate risky sexual behaviors. Studies that have observed associations between EDD and STD often examined Viagra use in very high risk men, including HIV positive MSM[15] or drug-abusing HIV prevention clinic attendees.[12] Very few of the men with NGU in our study were HIV positive and we did not specifically recruit drug users. The absence of an association between STD and EDD use in this population may also be due to our measure of EDD use. We only asked about lifetime EDD use, and therefore, it was not possible to ascertain whether EDD use occurred around the time of diagnosis. The use may have occurred several years prior to enrollment and thus would not be related to an STD diagnosed at enrollment into the study.

There were many strengths to this study. First, the study population was high risk and diverse and included both MSM and MSW. Additionally, the use of CASI to elicit most risk behaviors rather than interview/chart may have allowed for more accurate exposure measurements since CASIs typically elicit greater reporting of more stigmatized behaviors, such as drug use and risky sexual behaviors.[33] Furthermore, our assessment of STDs via medical records and tests performed at the time of enrollment was more precise than self-reported data and we were able to include more newly described STDs, such as *M. genitalium*.

There were also several limitations to this study. The study population consisted entirely of men who had NGU, and most causes of NGU are infectious agents that are likely sexually transmitted. Therefore, any association of EDD use with sexually transmitted organisms may have been attenuated or obscured by the presence of as-yet unidentified sexually transmitted pathogens. As this was a cross-sectional assessment, it was only possible to evaluate the

presence of associations rather than causal relationships. Our measure of EDD use did not differentiate between recreational and prescription use, and the reason for use is probably highly related to whether EDD use is accompanied by high risk behaviors and/or increased risk of STD. Finally, we lacked data on alcohol use, and this has been previously associated with many other risk behaviors, including drug use in general.

In conclusion, although EDD use in men with NGU was independently associated with several risk behaviors and sociodemographic characteristics (being MSM, older age, ecstasy use, higher annual income, and having multiple sex partners), it was not associated with either history of STDs or detection of prevalent STDs. Whether this is indicative of no increased risk of STD among EDD users, a result of imprecise measurement of the timing of EDD use relative to STD diagnosis or detection, or to the overall high likelihood of having a sexually transmitted pathogen among all men with NGU will require additional studies. Longitudinal approaches that capture the incidence of STDs and EDD use over time in populations with more heterogeneous distribution of sexually transmitted organisms, as well as those that differentiate between recreational and medical reasons for EDD use will be particularly useful.

Tables

Table 1. Characteristics of men with nongonococcal urethritis (NGU) attending the Public Health Seattle & King County (PHSKC) STD Clinic and participating in the *Mycoplasma genitalium* Antibiotic Susceptibility and Treatment (MEGA) study, by erectile dysfunction drug (EDD) use. Characteristics are presented as N (%).

			EDD Use				
	Total		Yes		No		P-value
	N=597		N=112 (18.8%)		N=485		
Age Category							
17-24	113	(18.9)	5	(4.5)	108	(22.3)	<0.001
25-34	242	(40.5)	36	(32.1)	206	(42.5)	
35-44	154	(25.8)	41	(36.6)	113	(23.0)	
45+	88	(14.7)	30	(26.8)	58	(12.0)	
Race							
White	328	(57.4)	75	(70.8)	253	(54.4)	0.02
Black	201	(35.2)	24	(22.6)	177	(38.1)	
Asian	20	(3.5)	2	(1.9)	18	(3.9)	
Pacific Islander	4	(0.7)	1	(0.9)	3	(0.6)	
Native American	4	(0.7)	1	(0.9)	3	(0.6)	
Multi/Other	14	(2.5)	3	(2.8)	11	(2.4)	
Hispanic	22	(3.8)	5	(4.5)	17	(3.6)	0.66
Sexual Orientation							
MSW	398	(66.7)	56	(50.0)	342	(70.5)	<0.001
MSM[a]	199	(33.3)	56	(50.0)	143	(29.5)	
Lifetime Drug Use							
Ecstasy: ever	205	(34.3)	54	(48.2)	151	(31.1)	0.001
Methamphetamine: ever	91	(15.2)	32	(28.6)	59	(12.2)	<0.001
Cocaine: ever	92	(15.4)	19	(17.0)	73	(15.1)	0.62
Education Level							
≤ High School/GED	265	(44.5)	37	(33.0)	228	(47.2)	0.008
> High School	330	(55.5)	75	(67.0)	255	(52.8)	
Yearly Income (CASI)							
< $10,000	207	(35.5)	26	(23.6)	181	(38.3)	<0.001
$10,000-29,999	196	(33.6)	29	(26.4)	167	(35.3)	
$30,000+	180	(30.9)	55	(50.0)	125	(26.4)	
Number Sex Partners (60 days)							
0	25	(4.2)	4	(3.6)	21	(4.3)	< 0.001
1	190	(31.9)	15	(13.4)	175	(36.2)	
2	161	(27.0)	28	(25.0)	133	(27.5)	
3+	220	(36.9)	65	(58.0)	155	(32.0)	
Vaginal Sex (60 days)	362	(65.8)	54	(51.9)	308	(69.1)	0.001
Anal Sex (60 days)	212	(38.6)	56	(53.9)	156	(35.1)	<0.001
Insertive Oral Sex (60 days)	446	(81.4)	96	(92.3)	350	(78.8)	0.001

Condom Use (60 days)							
Always	83	(17.3)	21	(23.6)	62	(15.8)	
Usually	134	(27.9)	22	(24.7)	112	(28.6)	0.20
Sometimes	113	(23.5)	25	(28.1)	88	(22.5)	
Never	151	(31.4)	21	(23.6)	130	(33.2)	

[a]"MSM" also includes men who had sex with both men and women (N=31, 5.2%)

Table 2. Characteristics of men with NGU attending the PHSKC STD clinic and participating in the MEGA study, by sexual orientation.

	Sexual Orientation				
	MSW N=398		MSM[a] N=199		P-value
Age Category					
17-24	83	(20.9)	30	(15.1)	
25-34	153	(38.4)	89	(44.7)	0.27
35-44	105	(26.4)	49	(24.6)	
45+	57	(14.3)	31	(15.6)	
Race					
White	171	(44.4)	157	(84.4)	<0.001
Non-White	214	(55.6)	29	(15.6)	
Hispanic	9	(2.3)	13	(6.6)	0.011
Lifetime Drug Use					
Ecstasy: ever	130	(32.7)	75	(37.7)	0.24
Methamphetamine: ever	52	(13.1)	39	(19.6)	0.04
Cocaine: ever	70	(17.6)	22	(11.1)	0.04
Education Level					
≤ High School/GED	210	(52.8)	55	(27.9)	<0.001
> High School	188	(47.2)	142	(72.1)	
Yearly Income					
< $10,000	165	(42.4)	42	(21.7)	
$10,000-29,999	121	(31.1)	75	(38.7)	<0.001
$30,000+	103	(26.5)	77	(39.7)	
Number Sex Partners (60 days)					
0	18	(4.5)	7	(3.5)	
1	161	(40.5)	29	(14.6)	<0.001
2	119	(30.0)	42	(21.1)	
3+	99	(25.0)	121	(60.8)	
Vaginal Sex (60 days)	341	(92.4)	21	(11.6)	<0.001
Anal Sex (60 days)	63	(17.1)	149	(82.3)	<0.001
Oral Sex (60 days)	271	(73.8)	175	(96.7)	<0.001
Condom Use (60 days)					
Always	45	(12.6)	38	(30.9)	
Usually	95	(26.5)	39	(31.7)	<0.001
Sometimes	89	(24.9)	24	(19.5)	
Never	129	(36.0)	22	(17.9)	

[a]"MSM" also includes men who had sex with both men and women in the past year (N=31, 5.2%)

Table 3. Crude and adjusted prevalence rations (PRs) for the association of EDD use and sociodemographic and behavioral risk factors, among men with NGU attending the PHSKC STD Clinic and participating in the MEGA study.

	Crude PR (95% CI)	Multivariable Adjusted PR[a]
Age Category		
17-24	Reference	Reference
25-34	3.36 (1.35-8.34)	2.63 (1.08-6.44)
35-44	6.01 (2.45-14.75)	5.00 (2.06-12.17)
45+	7.71 (3.12-19.06)	7.42 (3.01-18.29)
Race		
White	Reference	
Non-White	0.56 (0.38-0.82)	
Hispanic	1.20 (0.54-2.64)	
Sexual Orientation		
MSW	Reference	Reference
MSM[b]	2.00 (1.44-2.78)	1.41 (1.01-1.95)
Lifetime Drug Use		
Ecstasy: ever	1.78 (1.28-2.48)	2.17 (1.60-2.94)
Methamphetamine: ever	2.22 (1.58-3.14)	
Cocaine: ever	1.12 (0.72-1.74)	
Education Level		
≤ High School/GED	Reference	
> High School	1.63 (1.13-2.33)	
Yearly Income		
< $10,000	Reference	Reference
$10,000-29,999	1.18 (0.72-1.93)	1.01 (0.64-1.59)
$30,000+	2.43 (1.60-3.71)	1.70 (1.11-2.59)
Number Sex Partners (60 days)		
0-1	Reference	
2	1.97 (1.14-3.40)	
3+	3.34 (2.08-5.38)	
Multiple Partners (60 days)	2.76 (1.74-4.40)	2.10 (1.33-3.32)
Vaginal Sex (60 days)	0.56 (0.40-0.79)	
Anal Sex (60 days)	1.85 (1.31-2.62)	
Oral Sex (60 days)	2.74 (1.38-5.47)	
Condom Use (60 days)		
Consistent	Reference	
Inconsistent	0.68 (0.44-1.04)	

[a]Multivariable PR is adjusted for age category, sex of sex partners within past year (MSW or MSM), lifetime ecstasy use, yearly income, and having multiple partners in the past 60 days. Further adjustment for other characteristics had no appreciable effect on the multivariable PRs.

[b]"MSM" also includes men who had sex with both men and women (N=31, 5.2%)

Table 4. Univariable analyses of the association of EDD use and STD pathogens among men with NGU participating in the MEGA study

			EDD Use				
	Total N=597		Yes N=112 (18.8%)		No N=485		P-value
Any STD at Enrollment[a]	220	(36.9)	36	(32.1)	194	(40.0)	0.12
Bacterial STD at Enrollment[b]	221	(37.0)	34	(30.4)	187	(38.6)	0.10
Viral STD at Enrollment[c]	13	(2.2)	2	(1.8)	11	(2.3)	0.75
STD Diagnosis at Enrollment							
C. trachomatis	141	(23.6)	25	(22.3)	116	(23.9)	0.72
T. vaginalis	11	(1.8)	2	(1.8)	9	(1.9)	0.96
M. genitalium	79	(13.3)	9	(8.1)	70	(14.5)	0.09
U. urealyticum (biovar 2)[d]	141	(25.2)	20	(19.2)	121	(26.6)	0.24
HIV Positive	5	(0.8)	1	(0.9)	4	(0.8)	0.94
Herpes	8	(1.3)	1	(0.9)	7	(1.4)	0.65
Genital Warts	23	(3.9)	6	(5.4)	17	(3.5)	0.36
History of Any STD[e]	314	(54.5)	74	(67.3)	240	(51.5)	0.003
History of Bacterial STD[f]	292	(49.4)	68	(61.8)	224	(46.5)	0.004
History of Viral STD[g]	84	(15.0)	26	(24.3)	58	(12.8)	0.002
History of STD							
Chlamydia	204	(34.9)	47	(42.7)	157	(33.1)	0.06
Gonorrhea	171	(29.3)	47	(42.0)	124	(25.2)	0.001
HIV Positive	9	(1.6)	5	(4.6)	4	(0.9)	0.02
Herpes	73	(12.6)	21	(19.3)	52	(11.1)	0.02
Genital Warts	66	(11.4)	19	(17.6)	47	(10.0)	0.02
Syphilis	24	(4.2)	10	(9.4)	14	(3.0)	0.003

[a]Includes detection of *C. trachomatis*, *T. vaginalis*, *M. genitalium*; and/or new diagnosis of HIV or herpes at enrollment

[b]Includes detection of *C. trachomatis*, *T. vaginalis*, or *M. genitalium* at enrollment

[c]New diagnosis of HIV or herpes at enrollment only

[d]*U. urealyticum* biovar 2 is the specific species, differentiated from *U. parvum,* both of which were formerly referred to as *U. urealyticum*

[e]Includes a past diagnosis of chlamydia, gonorrhea, syphilis, HIV, or herpes

[f]Includes a past diagnosis of chlamydia, gonorrhea, or syphilis

[g]Includes a past diagnosis of HIV or herpes

Table 5. Crude and adjusted PRs for the association of EDD use and STD, among men with NGU participating in the MEGA study.

	Crude PR	Adjusted PR
Any STD at Enrollment[a]	0.80 (0.60-1.07)	--*
Bacterial STD at Enrollment[b]	0.79 (0.58-1.06)	--*
C. trachomatis at Enrollment[c]	0.93 (0.64-1.37)	1.10 (0.70-1.72)
M. genitalium at Enrollment[d]	0.56 (0.29-1.08)	0.74 (0.38-1.44)
HIV at Enrollment[e]	1.08 (0.12-9.61)	0.43 (0.05-3.73)
Herpes at Enrollment[f]	0.62 (0.08-4.99)	3.51 (0.14-91.0)
Viral STD at Enrollment[g]	0.79 (0.18-3.50)	0.88 (0.18-4.38)
History of Any STD[h]	1.31 (1.00-1.70)	1.14 (0.97-1.34)
History of Bacterial STD[i]	1.33 (1.10-1.53)	1.16 (0.97-1.39)
History of Viral STD[j]	1.89 (1.25-2.89)	1.28 (0.83-1.96)

*None of the potentially confounding characteristics that were evaluated appreciably changed the PRs for the association of any STD or any bacterial STD at enrollment; therefore only crude PRs are presented

[a]Includes detection of *C. trachomatis*, *T. vaginalis*, or *M. genitalium* at enrollment; includes new diagnosis of HIV or herpes at enrollment

[b]Includes indication of *C. trachomatis*, *T. vaginalis*, or *M. genitalium* at enrollment

[c]PR estimate adjusted for age

[d]PR estimate adjusted for income and race

[e]PR estimate adjusted for sexual orientation, race, and number of sex partners in the past 60 days

[f]PR estimate adjusted for age, sexual orientation, and income

[g]Includes new diagnosis of HIV or herpes at enrollment; PR estimate adjusted for age and race

[h]Includes a past diagnosis of chlamydia, gonorrhea, syphilis, HIV, or herpes; PR estimate adjusted for age

[i]Includes a past diagnosis of chlamydia, gonorrhea, or syphilis; PR estimate adjusted for age

[j]Includes a past diagnosis of HIV or herpes; PR estimate adjusted for age and sexual orientation

References

1. Erectile Dysfunction. Mayo Clinic. http://www.mayoclinic.org/diseases-conditions/erectile-dysfunction/basics/definition/con-20034244. Published 2015. Accessed December 1, 2015.
2. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med*. 2007;120(2):151-157.
3. Capogrosso P, Colicchia M, Ventimiglia E, et al. One patient out of four with newly diagnosed erectile dysfunction is a young man--worrisome picture from the everyday clinical practice. *J Sex Med*. 2013;10(7):1833-1841.
4. FDA approves Stendra for erectile dysfunction. US Food and Drug Administration Press Releases. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302140.htm. Published 2012. Accessed December 1, 2015.
5. Goltz HH, Coon DW, Catania J a, Latini DM. A pilot study of HIV/STI risk among men having sex with men using erectile dysfunction medications: challenges and opportunities for sexual medicine physicians. *J Sex Med*. 2012;9(12):3189-3197.
6. Bechara A, Casabé A, De Bonis W, Helien A, Bertolino MV. Recreational use of phosphodiesterase type 5 inhibitors by healthy young men. *J Sex Med*. 2010;7(11):3736-3742.
7. Cook RL, McGinnis K a., Samet JH, et al. Erectile dysfunction drug receipt, risky sexual behavior and sexually transmitted diseases in HIV-infected and HIV-uninfected men. *J Gen Intern Med*. 2010;25(2):115-121.
8. Chu PL, McFarland W, Gibson S, et al. Viagra use in a community-recruited sample of men who have sex with men, San Francisco. *J Acquir Immune Defic Syndr*. 2003;33(2):191-193.
9. Harte B, Meston C. Recreational use of erectile dysfunction medications in undergraduate men in the United States: Characteristics and Associated Risk Factors. *Arch Sex Behav*. 2011;40(3):597-606.
10. Cachay E, Mar-Tang M, Mathews WC. Screening for potentially transmitting sexual risk behaviors, urethral sexually transmitted infection, and sildenafil use among males entering care for HIV infection. *AIDS Patient Care STDS*. 2004;18(6):349-354.
11. Swearingen SG, Klausner JD. Sildenafil use, sexual risk behavior, and risk for sexually transmitted diseases, including HIV infection. *Am J Med*. 2005;118(6):571-577.
12. Fisher DG, Malow R, Rosenberg R, Reynolds GL, Farrell N, Jaffe A. Recreational Viagra use and sexual risk among drug abusing men. *Am J Infect Dis*. 2006;2(2):107-114.
13. Carey JW, Mejia R, Bingham T, et al. Drug use, high-risk sex behaviors, and increased risk for recent HIV infection among men who have sex with men in Chicago and Los Angeles. *AIDS Behav*. 2009;13(6):1084-1096.
14. Mansergh G, Shouse RL, Marks G, et al. Methamphetamine and sildenafil (Viagra) use are linked to unprotected receptive and insertive anal sex, respectively, in a sample of men who have sex with men. *Sex Transm Infect*. 2006;82(2):131-134.
15. Kim A, Kent C, Klausner J. Increased risk of HIV and sexually transmitted disease transmission among gay or bisexual men who use Viagra, San Francisco 2000–2001. *AIDS*. 2002;16(10):1425-1428.
16. Wong W, Chaw JK, Kent CK, Klausner JD. Risk factors for early syphilis among gay and bisexual men seen in an STD clinic: San Francisco, 2002-2003. *Sex Transm Dis*. 2005;32(7):458-463.
17. Jena AB, Goldman DP, Kamdar A, Lakdawalla DN, Lu Y. Sexually transmitted diseases

among users of erectile dysfunction drugs: analysis of claims data. *Ann Intern Med*. 2010;153(1):1-7.

18. Spauwen LWL, Niekamp A-M, Hoebe CJPA, Dukers-Muijrers NHTM. Drug use, sexual risk behaviour and sexually transmitted infections among swingers: a cross-sectional study in The Netherlands. *Sex Transm Infect*. 2015;91(1):31-36.
19. Dunlop EM, Harper I a, al-Hussaini MK, et al. Relation of TRIC agent to “non-specific genital infection.” *Br J Vener Dis*. 1966;42(2):77-87.
20. Manhart LE, Gillespie CW, Lowens MS, et al. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: A Randomized Controlled Trial. *Clin Infect Dis*. 2013;56(7):934-942.
21. Ondondo R, Whittington W, Astete S, Totten P. Differential association of ureaplasma species with non-gonococcal urethritis in heterosexual men. *Sex Transm Dis*. 2010;86(4):271-275.
22. Martin D. Urethritis in males. In: Holmes K, Sparling P, Stamm W, eds. *Sexually Transmitted Diseases*. New York: McGraw Hill; 2008:1107-1126.
23. Manhart LE, Mostad SB, Baeten JM, Astete SG, Mandaliya K, Totten P a. High Mycoplasma genitalium organism burden is associated with shedding of HIV-1 DNA from the cervix. *J Infect Dis*. 2008;197(5):733-736.
24. Mansergh G, Colfax GN, Marks G, Rader M, Guzman R, Buchbinder S. The Circuit Party Men’s Health Survey: findings and implications for gay and bisexual men. *Am J Public Health*. 2001;91(6):953-958.
25. Crosby R, Diclemente RJ. Use of recreational Viagra among men having sex with men. *Sex Transm Infect*. 2004;80(6):466-468.
26. Boyd CJ, McCabe SE, D’Arcy H. Ecstasy use among college undergraduates: Gender, race and sexual identity. *J Subst Abuse Treat*. 2003;24(3):209-215.
27. Corliss HL, Rosario M, Wypij D, Sarah a, Frazier a L, Austin SB. Sexual orientation and drug use in a longitudinal cohort study of U.S. adolescents. *Addict Behav*. 2011;35(5):517-521.
28. Koblin B a, Husnik MJ, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. *Aids*. 2006;20(5):731-739.
29. Travison TG, Hall S a., Fisher W a., et al. Correlates of PDE5i use among subjects with erectile dysfunction in two population-based surveys. *J Sex Med*. 2011;8(11):3051-3057.
30. Brown AH, Domier CP, Rawson RA. Stimulants, Sex, and Gender. *Sex Addict Compulsivity*. 2005;12(2-3):169-180.
31. Fisher DG, Reynolds GL, Ware MR, Napper LE. Methamphetamine and viagra use: Relationship to sexual risk behaviors. *Arch Sex Behav*. 2011;40(2):273-279.
32. Korkes F, Costa-matos A, Gasperini R, Reginato P V., Perez MDC. Recreational use of PDE5 inhibitors by young healthy men: Recognizing this issue among medical students. *J Sex Med*. 2008;5(10):2414-2418.
33. Newman JC, Jerlais Des D, Turner F. The differential effects of face-to-face and computer interview modes. *Am J Public Health*. 2002;92(2):294-297.