Sex, Drugs, and Clinical Research

By Jennifer R. Fishman

The images of the two machines presented in this article (pp 14–15) were inspired by a slide that has been projected several times over the past year or so, at various women's health research congresses. The congress speakers invariably explain that the first machine, depicted as a large rectangular box with a single on-off switch and indicator light, represents male sexuality. The second machine, identical in size and shape but almost completely covered with various switches, knobs, levers, buttons, and colored indicator lights, represents female sexuality. It is incidentally revealed that Pfizer Incorporated, the makers of Viagra™, had distributed the slide to presenters. At each presentation of the slide, the audience laughs knowingly. Everyone gets the joke.

The juxtaposition of the two machines is effective as a presentation tool, requiring little explanation, yet speaking volumes about our taken-for-granted ideas about sexuality. The joke, so readily understood by members of the audience, also challenges us to consider how our culturally informed notions about sexuality inform contemporary research on sexual dysfunctions. The cartoon relies on the belief that male sexuality is simple, whereas female sexuality is complicated.

But what if we examine assumptions such as this one, laying bare what is usually only tacitly acknowledged, in order to determine how they become part of scientific research and the development of new biomedical technologies? The imagery, after all, is more than just an in-joke among sexual dysfunction researchers. It shows that cultural assumptions about men and women are ingrained even among the professionals who not only develop drugs, but also shape our understanding of sexual dysfunction and its treatment.

Comparison of the clinical testing of Viagra on men and women may allow us to examine the ways in which our cultural conceptions about the nature of sexuality play a role in determining the potential success of the drug. In the process of developing and choosing methods and measurements to evaluate sexual arousal, researchers contribute to the very definition of the objects they study. The assumption that male sexuality is simple, and that female sexuality is complicated, becomes incorporated into research hypotheses, and in turn affects the way that men's and women's sexual problems are understood, classified, and treated.

Equal but Different

Sildenafil citrate, marketed and sold by Pfizer under the brand name Viagra, is an oral therapy developed for the treatment of erectile dysfunction (ED). Viagra was approved by the U.S. Food and Drug Administration in March 1998, and is considered the first noninvasive, nonsurgical medical treatment for this health problem. Prior to the development of Viagra, the medical treatment options available for impotence were limited to penile implants, vacuum pumps, injectables, and suppositories placed into the urethra. Although these options remain available, they are regarded as far less appealing than oral medication and are generally employed only after Viagra fails to produce desired results. Available only by prescription, Viagra produces increased blood flow into certain areas of the penis by enhancing the smooth muscle relaxant effects of nitric oxide, released in response to sexual stimulation. The blue diamond-shaped tablets are ingested orally, take effect within twenty to sixty minutes, and remain effective for two to four

hours. Pfizer defines "effectiveness" to mean that, after taking Viagra, a previously impotent man will be able to "achieve and sustain" an erection *if and when* sexually stimulated *(1)*.

During its clinical trials, Viagra was administered to over 3000 male patients, nineteen to eighty-seven years of age, with ED of various etiologies (organic, psychogenic, mixed). The effectiveness of Viagra was evaluated through several self-report assessment instruments, including the International Index of Erectile Function (IIEF) that was developed expressly for the Viagra trials *(2)*. This instrument was designed to elicit self-report responses about erectile function, including the ability to achieve erections sufficient for sexual intercourse and the maintenance of erection after penetration *(2, 3)*. Heterosexual, monogamous men took Viagra at home and filled out an index of questions that asked them to assess the quality of their erections *(4)*.

These clinical trials relied on the assumption that male sexuality was clear and simple. There was no question about *what* to measure, *how* to measure it, or *why* to measure it. Male sexual arousal was equated with the presence of an erection, and drug-mediated erections were equated with the solution to male arousal problems. In a compilation of data from four double-blind, randomized fixed-dose response studies of a total of 1,797 patients, sixty-three to eighty-two percent of men (depending on the dose of Viagra given) reported improvement in their erections, compared to twenty-four percent of men on placebo *(1)*.

With such promising trial results, Viagra received substantial advance press prior to its commercial release, and within a short time became the most commercially successful clinical drug on record. Four years later, it is still selling strong. Seeing advantages in touting the drug's popularity, Pfizer introduced the slogan Four Tablets Dispensed Every Second, which now appears on promotional products (e.g., pens, post-it notes, pads of paper) given away to clinicians. Sales volume thus became both a marketing tool and a sign of efficacy: the seventeen million tablets dispensed to sixteen million men seemed to "prove" that Viagra is the answer to men's sexual problems *(5)*. The marketing strategies also seem to support the assumption that all male sexual problems (at least sixteen million men's worth) are reducible to the presence or absence of an erection.

Viagra's success as a drug for ED spawned a considerable amount of interest in the diagnosis and treatment of both male and female sexual dysfunction. In the months following its approval, researchers turned their attention to Viagra's effects on women, often framing their arguments in terms of equity.

Can Viagra™ work for women? We still don't know. As Jennifer Fishman shows, sociological criticism of the conduct and conclusions of research may offer a perspective from which clinical practices can be more broadly questioned and, ultimately, improved.

Specifically, they argued that women's sexual problems had been neglected by the medical community and required the same consideration as had been shown for ED. Further fueling interest, a sex survey that appeared in *JAMA* reported that up to forty-three percent of all women might suffer from some form of sexual dysfunction *(6)*. Although it was never suggested that the origins of these "dysfunctions" were solely (or even partly) organic, this figure has traveled widely and is often used as the justification for further biomedical research and intervention into female sexual dysfunction *(7–9)*. Thus, a new area of research in sexual health medicine was launched: the diagnosis and treatment of female sexual dysfunction (FSD) *(10)*.

Initially, hopes that Viagra might work for women rested on the assumption that men's and women's bodies, despite their obvious anatomical differences, might share fundamental aspects of sexual physiology. In order to "treat" women with Viagra, the biochemical effects of nitric oxide that lead to arousal in men had to be presumed for women. Furthermore, women's sexual arousal, like men's, had to be viewed as a simple physical and physiological reaction to sexual stimuli. Nevertheless, when it came to designing studies to test the effectiveness of new treatments for FSD, researchers reconsidered the assumed similarities and differences between men's and women's sexual functioning. Consequently, many of the initial studies to determine the physiological effects of Viagra on females were conducted not on humans, but rather on animals.

Moreover, those researchers who were willing, at least temporarily, to presume the involvement of nitric oxide and investigate Viagra's efficacy directly in women would still have to determine how efficacy could be gauged. Unlike the clinical trials on men, where an erection was deemed an unambiguous, simple, and outwardly visible sign of male sexual arousal, female sexual arousal did not seem to have a straightforward indicator. Researchers had to define the object of inquiry: *What* is female sexual arousal and how is it measured? Amount of vaginal lubrication? Increased vaginal blood flow? Clitoral engorgement? Increased genital sensitivity? What is the female equivalent of the male erection?

A panoply of technologies were utilized to measure aspects of arousal in the laboratory: vaginal blood flow was tractable through use of the vaginal photoplethysmograph; vaginal lubrication was indicated by pH; a biothesiometer measured genital vibratory and temperature perception thresholds; clitoral blood flow and engorgement could now be monitored by MRI. Curiously, although such studies were

intended to demystify female sexuality by reducing arousal to a single indicator, the ensuing controversy over alternative measurements in many ways reinforced the traditional assumption that female sexuality is "complicated."

The very fact that these studies tended to use laboratory measurements, rather than utilizing a self-report index, bespeaks the assumption of a "complicated" female sexual response. And even though some studies *(11, 12)* did incorporate a self-report component such as the Female Sexual Function Index *(13)*, the self-reported data were viewed skeptically. Unlike male subjects, who were deemed capable of ascertaining their own physiological response to Viagra, female patients could apparently not be trusted, whether in the laboratory or in the privacy of their own bedrooms, to assess the more elusive indicators of female sexual arousal. To date, there have been no unequivocally successful (i.e., double-blind, placebo-controlled) published studies of Viagra on women.

From Physiology to Psychology

The controversy over measuring women's sexual arousal fueled speculation not only that female sexuality might be *physiologically* more complicated than male sexuality, but also that women might in fact be *psychologically* more complicated as well. Specifically, a "desynchrony" was posited to exist between women's physiological genital arousal (i.e., changes objectively documented in the laboratory) and subjective arousal (i.e., the conscious experience of arousal). In research that predates the Viagra trials, women's assessments of their own sexual arousal problems (i.e., reports of not feeling aroused in the presence of sexual stimulation) did not always correspond with clinical measurements of arousal. For example, women diagnosed with female sexual arousal disorder based on diagnostic interviews failed to show diminished vaginal blood flow, relative to the healthy control group, when sexually stimulated in the laboratory *(14, 15)*.

This research raises a fundamental question about the *validity* of the laboratory measurements used in sexual arousal studies: Were researchers accurately and correctly measuring the phenomenon in question, that is, sexual arousal? Or might it be that the laboratory techniques in fact gave accurate indicators of arousal, but that women fail to recognize their own arousal? Despite multiple research efforts, a definition of female arousal remained elusive.

For men in laboratory studies, there has been no such apparent "desynchrony," but rather there has been high correlation between genital arousal and subjective arousal. When men were exposed to visual sexual stimulation and asked to push a button when they felt aroused, studies showed that this corresponded within seconds to the measurable presence of an erection *(16)*. Indications of the phenomenon of desynchrony in women date back to earlier sexology research, in which women claimed not to be aroused by pornographic visual materials, even though, in the laboratory, physiological arousal was documented. In these older studies, subjective assessments of arousal were discounted, whereas "genital physiological arousal" was championed, such that the use of visual erotic stimuli has consequently persisted in the laboratory ever since.

As researchers attempt to show the clinical efficacy of drugs, the discrepancy between subjective arousal and physiological arousal has become an area of concern, as it has confounded and obscured clinical trial results. In subsequent clinical studies of Viagra, there have been attempts to classify the clinical population of women by distinguishing "genital" from "subjective" arousal disorders, and then including only those women with genital arousal disorders (as documented through physiological tests) in trials. Furthermore, there is the hope that with continued research, a Viagra-responsive sub-population will be found. In a case of "reverse engineering," this may in turn tell us something about the etiology of arousal disorders.

From Arousal Problems to Desire Disorders

It is not yet entirely clear whether a subpopulation of women with "genital" (i.e., objectively demonstrable) arousal disorders exists. In any case, such a subpopulation would seem to be small; indeed, reports of women with arousal problems, in general, pale in comparison to what is considered the more prevalent subtype of FSD, namely, hypoactive sexual *desire* disorder. Unlike men, whose most commonly reported sexual problem is ED, women do not report that they *can't* have sex, just that they don't *desire* it. Some statistics estimate that between eleven and sixteen million women may have a sexual desire disorder. According to the *JAMA* study (see above; *6*) thirty-three percent of all women may have some form of sexual desire disorder. This reportedly high percentage has, unsurprisingly, inspired an increasing amount of biomedical attention.

Interestingly, the bulk of newer research has focused on the use of testosterone and other androgen therapies to treat women with hypoactive sexual desire disorder *(17)*. Thus, in another attempt to find a simple model for female sexuality, researchers have turned their attention to the search for a pharmacological solution to women's lack of desire. As part of a larger trend in psychiatry and behavioral medicine, women's sexual problems, once conceived of as psychological in nature, are now being redefined as a biochemical imbalance or deficiency. It is no longer women's *minds* that are the targets for intervention, but rather their *brains*. New neuroscientific research transforms "desire" into a biological phenomenon, raising a host of scientific questions: Where are the origins of sexual desire? How can it be endogenously triggered? What is the neuroscience and biochemistry of desire? How does female desire differ from male desire?

The Difference That Difference Makes

The very different trajectories that research has followed into female as opposed to male sexual dysfunction have led to very different conceptions of the nature of the disorders. ED, particularly with the advent of Viagra, has been conceptualized primarily as a problem of organic origin, one of physiological mechanics and hydraulics. In part due to the absence of a clear, measurable anatomical response such as an erection, and in part because Viagra has not been substantiated as an answer to women's sexual problems, FSD has been framed as a complicated puzzle, with efforts moving away from assessing genital functioning. The apparent simplicity of male sexuality has thus furthered the notion that men's bodies are ideal objects for research into sexual desire as well as arousal. The supposed complexity of female sexuality has further solidified the idea that women's bodies are messy and imperfect.

The drive for simple models in scientific research has shaped our conceptualization of sexual dysfunction and its treatment, which has in turn shaped our conceptualization of men's and women's bodies and potentials. Because it was already assumed that male sexuality was simple—like a machine with a single switch— scientific models of male sexual arousal were reduced to a single indicator, the erection. But in the assumption of simplicity, what complexities about male sexuality have been ignored or undervalued? For instance, has Viagra's ability to create erections resulted in greater sexual satisfaction for men? And if researchers had looked for alternative measures of male sexual arousal, would they have found them? Conversely, what if female sexuality had been presumed to be simple from the outset? Perhaps then, researchers might have simply asked women about their own responses, and the debate over laboratory measures would have been moot.

Although scientific research, hypotheses, methods, and measures are construed with the aim of objectivity, scientific data ultimately rest on the knowledge (and limitations) of human researchers. This knowledge includes cultural assumptions that are assimilated into both the researchers' perspectives and their questions. How scientific objects are defined at the outset can restrict the range of possible outcomes, thereby influencing not only how problems continue to be refined by clinicians over the long term, but also how patients conceptualize their own difficulties and seek treatment. Examination and consideration of the assumptions that undergird clinical research can perhaps lend greater insight into the framing of research questions, the methods and measurements chosen, and the very definitions of the objects of inquiry.

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Jennifer R. Fishman is a doctoral candidate in Sociology in the Department of Social and Behavioral Sciences at the University of California, San Francisco. Her dissertation is a sociohistorical analysis of sexual dysfunction in the Viagra and post-Viagra era of biomedical, biotechnological, and pharmaceutical research. E-mail jfishma@itsa.ucsf.edu; fax 415-476-6552.