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Sex–Gender Differences in Drug Abuse: A Shift in the Burden of Proof?

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In the early years of NIDA-supported drug abuse research, much of the research on women was treatment related and conducted out of concern for their pregnancy status. Since then, drug abuse research on women has expanded to include females of all ages, including infants, children, and adolescents, both human and animal. This expansion has also extended to the study of male–female differences. In the early years of the expansion, National Institutes of Health study sections demanded a heavy burden of proof from drug abuse researchers who proposed to study male–female differences. The need for such research appeared not to have face validity. The tide has now changed with the growing body of literature attesting to its scientific and clinical validity. This change is often reflected in concerns expressed in study sections reviewing drug abuse grant applications that an applicant does not propose to analyze the data for sex–gender differences when in fact the literature suggests that such differences would be observed. Although the change has been slow, it suggests that the burden of proof is shifting from having to defend why sex–gender differences should be studied to having to defend why they should not.

Keywords: drug abuse, sex differences, gender differences, women, conclusion errors

This issue of *Experimental and Clinical Psychopharmacology* contains four articles addressing research on the relationship between progesterone and drug abuse, as well as an article addressing the use of progesterone in clinical research. The five articles on drug abuse research are based on a symposium, organized by Rajita Sinha (Yale University) and Nancy Mello (Harvard University), entitled "Progesterone Effects on Stress and Cocaine Intake: Translations From the Laboratory to the Clinic," held at the Annual Meeting of the College on Problems of Drug Dependence (CPDD) in Quebec City, Quebec, Canada, June 16–21, 2007. It is noteworthy that this research likely could not have been conducted until recent years, not because of a lack of methodological approaches, but rather because of a change in attitudes on research on sex–gender differences that has been gradually occurring over the past 15 years. This change in attitudes has laid the groundwork for the importance of this line of investigation addressing male–female differences in drug abuse and the role of gonadal hormones. This article addresses that change, from the perspective of both grant-funding efforts of the National Institute on Drug Abuse (NIDA) and the scientific development of the field.

Since its establishment in 1974, NIDA has demonstrated a commitment to supporting research on drug abuse in women. The early focus of this effort in the 1970s and 1980s was largely on the unique treatment needs of women. Of particular concern were pregnant women and the possible adverse effects of prenatal exposure to abused drugs on pregnancy outcome and the developing child. In the 1970s and early 1980s, this focus was largely on opiate-dependent women. The increase in cocaine use in the mid- and late 1980s generated public concern over cocaine use by pregnant women and led to major NIDA funding initiatives to support research on the development and enhancement of treatment services for drug-abusing pregnant and postpartum women. In addition, in the mid-1980s, the growing recognition of the intersection of HIV/AIDS and drug abuse and the unique issues facing women led to NIDA initiatives to support HIV/AIDS research on women, especially risk factors, natural history, and interventions. NIDA's commitment to support drug abuse research on pregnant and postpartum women and research on HIV/AIDS and women continues today.

In the mid-1990s, NIDA's commitment to the study of women was expanded to include the study of male–female differences in drug abuse. One of the factors associated with this shift was the issuance of guidelines in 1994 from the National Institutes of Health (NIH) requiring the inclusion of women and minorities in NIH-funded human research and requiring gender analysis in Phase 3 clinical trials. Also, in 1994, NIDA convened a conference, "Drug Addiction Research and the Health of Women," which reviewed the progress and gaps in research on women in drug abuse. It was apparent from that meeting that there were three significant areas in which NIDA needed to expand its research efforts on women: (a) to study females of all ages, not just

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those of child-bearing age, (b) to study male–female differences across all ages, and (c) to conduct that research in both humans and animals.

Since 1994, NIDA has been actively engaging in a variety of efforts to infuse the study of issues specific to women (including females of all ages) and sex–gender differences in all areas of drug abuse research. The expansion of research on women to include sex–gender differences is a crucial complement to the study of issues specific to women. Studying outcomes separately in males and females expands our knowledge regarding women and drug abuse beyond those issues that are specific to women to include all areas of drug abuse and not just issues specific to women. In essence, the study of sex–gender differences is a more comprehensive approach that, in fact, encompasses issues specific to women because such issues, by definition, are sex–gender differences. Moreover, this approach advances our knowledge base on drug abuse in males as well. In addition, as discussed later, this sex–gender-based approach to conducting drug abuse research guards against serious conclusion errors regarding both men and women.

In research on differences between males and females, the terms *sex* and *gender* are often used interchangeably. In the 2001 Institute of Medicine report, "Exploring the Biological Contributions to Human Health: Does Sex Matter?" *sex* is defined as,

> the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement, and *gender* as a person's self-representation as male or female, or how that person is responded to by social institutions on the basis of the individual's gender presentation. Gender is shaped by environment and experience. (Institute of Medicine, 2001, p. 1)

Thus, according to these definitions, sex is a biological construct and gender is a psychosocial construct. In research with humans, however, because of the dynamic interplay between biology and the psychosocial environment, it is often unknown a priori whether the origin of a given male–female difference is sex-based, gender-based, or both, and, indeed, the search for those origins is an essential research goal. In nonhuman animal research, *sex difference* is the preferred term.

Fertilizing and Growing the Field of Research on Women and Sex–Gender Differences

NIDA's efforts to promote research on women-specific issues and sex–gender differences have included several overlapping strategies. Included in these efforts, some of which are highlighted below, are funding opportunity announcements (e.g., program announcements and requests for applications), special programs targeting the next generation of researchers, clinical trials initiatives, sponsorship of events at scientific conferences, scientific presentations, publications, and collaborations with other entities within the Department of Health and Human Services (DHHS) as well as nongovernmental entities.

Issuance of funding opportunity announcements is an important way in which NIDA has sought to promote research in this area, and over the years, there have been many initiatives that target unique aspects of drug abuse in women or subgroups of women, such as pregnant and postpartum women, women with or at risk for HIV/AIDS, minority women, and other underserved women. In addition, NIDA has released announcements that specifically target research on sex–gender differences, including the recently announced availability of competitive grant supplements to study sex–gender differences in drug abuse. The supplements provide funds to (a) increase the sample size of human studies to provide statistical power for a gender analysis of the data, (b) add females to male-only animal studies to permit a male–female comparison of outcomes, and (c) conduct a gender analysis within a secondary data analysis.

An important way to promote the long-term development of this area is to target researchers who are early in their career, from graduate or medical school through the early years after doctoral and postdoctoral training. Since 1999, NIDA has sponsored a travel award program for individuals in this targeted group who present their work on women or sex–gender differences at annual meetings of the CPDD. In addition, grant support specifically targeting this group includes a program announcement to support dissertation research and an initiative with the NIH Office of Research on Women's Health (ORWH) targeting junior faculty (see below).

The Center for Clinical Trials Network (CCTN) at NIDA is playing an important role in advancing research on women and male–female differences. The CCTN partners with extramural grantees through 17 U10 grants to form the Clinical Trials Network (CTN), which consists of 17 regional research and training centers at academic medical centers across the United States that are affiliated with 240 community treatment programs. The CTN has implemented several clinical trial protocols specific to women and created a special publication targeted at the recruitment and retention of women in drug abuse clinical trials, and, of course, data from Phase 3 clinical trials are analyzed by gender. The CTN's Women's Special Interest Group, created in 2001 and composed of researchers and clinicians, serves an advocacy role in developing gender-based research approaches within CTN protocols.

Presentations on women and sex–gender differences at scientific conferences is an important mechanism for encouraging more research in this area. NIDA staff have organized symposia and made presentations on women and sex–gender differences at a wide variety of scientific conferences, including the following: Alcohol and Drug Problems Association of North America, American Psychiatric Association, American Psychological Association, American Society of Addiction Medicine, American Society for Pharmacology and Experimental Therapeutics, Association of Alcoholism and Substance Abuse Providers of New York State, California Society of Addiction Medicine, CPDD, Conference on Sex and Gene Expression, International Council on Alcohol and Addictions, North Carolina Governor's Institute on Alcohol and Substance Abuse, Substance Abuse Librarians and Information Specialists Conference, Society for Research on Child Development, Soci-

ety for Research on Nicotine and Tobacco, Society for Neuroscience, Society for Prevention Research, World Congress on Women's Mental Health, and the Virginia Summer Institute for Addiction Studies.

Creating publications on women and sex–gender differences is another means by which NIDA advocates for research in this area. These publications have ranged from NIDA monographs to frequent articles in NIDA's newsletter, *NIDA Notes*. In 1996, NIDA began publication of *Articles That Address Women's Health and Gender Differences: A Collection From NIDA Notes*, which is a compilation of research articles from *NIDA Notes*. It has been updated five times since 1996, most recently in October of 2006. Yearly since 1999, NIDA has published *Focus on Women & Sex/Gender Differences: Mini-Program* for distribution at the CPDD annual conference. Excerpted from the CPPD program book, this mini-program contains only those program listings related to women and sex–gender differences. It also contains the CPDD abstracts on these topics and information about the annual Women and Gender Junior Investigator Travel Awardees supported by NIDA. These and other publications are located on the Women and Gender site on NIDA's Web site home page. This site, which was created in 1998, also lists funding opportunities in this area as well as other resources.

NIDA has partnered with various entities within the DHHS on meetings, scientific presentations, and publications. These groups have included the DHHS Office on Women's Health, the Office of the Surgeon General, the Health Resource and Services Administration, the ORWH, the National Cancer Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Child Health and Human Development, the National Institute of Mental Health, National Institute of Neurological Disorders and Stroke, and the Substance Abuse and Mental Health Services Administration. NIDA has also partnered with nongovernmental organizations on meetings, scientific presentations, and publications, including the National Center on Addiction and Substance Abuse at Columbia University, the Smithsonian Institution, and the Society for Research on Women's Health.

NIDA's efforts to promote research on women and sex–gender differences have been greatly enhanced by participation in several initiatives issued by the ORWH, which was established in 1990 within the Office of the NIH Director. One of ORWH's early initiatives was to provide funds to the NIH Institutes and Centers (ICs) for administrative supplements to NIH-funded grants to encourage researchers to conduct research on women's health. Through that initiative, not only did ORWH provide supplemental funds for several NIDA grants, but NIDA also contributed major funding that significantly increased the total number of awarded supplements. In 1996, ORWH initiated their Research Enhancement Awards Program (REAP) initiative, in which they invited ICs to identify nonfunded grant applications that were rated highly by NIH study sections but missed the IC funding line and to nominate those applications for first year funding by ORWH. ICs, in turn, also provided cofunding and commitment to fully fund the remaining years of the grant period. Over the years of the REAP initiative, which ends this year, NIDA has been an active participant, receiving ORWH cofunding for numerous grants that otherwise would not have received funding during that fiscal year.

Another ORWH initiative for which NIDA has been a cosponsor and cofunder is the P50 Center Grant Program, "Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health," which was funded initially in 2000, was recompeted this year, and will result in funding of 11 P50 SCORs across various NIH ICs. Three of the 11 SCORs focus on sex–gender differences in drug abuse and are located at the Medical University of South Carolina, the University of Miami, and Yale University. Another ORWH initiative in which NIDA has actively participated is the "Building Interdisciplinary Research Careers in Women's Health" program. Over the years of this program, initiated in 2000, it has provided funds for protected research time and mentoring of junior-level faculty members at the Virginia Commonwealth University, the University of Kentucky, Yale University, and, beginning this year, the Medical University of South Carolina.

NIDA's most recent collaboration with ORWH is with the Advancing Novel Science in Women's Health Research program. Released on June 11, 2007 (initially as a 3-year program), this program announcement has set aside funds for a once-yearly receipt date to fund grants on women and sex–gender differences, both human and animal research, under the NIH R03 Small Grant mechanism and the R21 Exploratory/Developmental Award mechanisms.

Growth of Research on Sex–Gender Differences

Within NIH study sections, the importance of research addressing drug abuse issues specific to women has always had face validity; however, this has not been true for research on male–female differences in drug abuse. Fortunately, over the past 15 years, there has been significant improvement in priority scores for such applications. Previously, their summary statements were likely to include the comment that there was inadequate rationale to study male–female differences. The sheer absence of research on male–female differences did not have face validity. This reflected the implicit assumptions, presumably held by the wider scientific community, that sex–gender does not matter in drug abuse and that any important male–female differences related only to female reproductive function and therefore were of no theoretical, clinical, or practical importance outside the realm of reproduction. More generally, there was the view that, "if there are important male–female differences in drug abuse, we would have known about them by now," a view that failed to recognize that perhaps such knowledge was lacking because research had not addressed it! Thus, the situation for researchers interested in studying sex–gender differences in drug abuse was often a catch-22. Their persistence, however, eventually paid off, and applications in this area gradually began receiving better priority scores, yielding increasing numbers of NIDA-funded grants and publications in this area. The

growing numbers of publications are reflected in Figure 1, which shows the number of articles cited in PubMed for the four 5-year periods from 1987–2006 based on searching on the term *gender differences* plus the terms *drug abuse*, *drug dependence*, *drug addiction*, and *smoking*. The hits for the first 5-year period, 1987–1991, ranged from 64 to 89. They increased over the next three 5-year periods, and in the last 5-year period ranged from 439 to 488.

There is now ample evidence that circulating female reproductive hormones play a role in drug abuse beyond the reproductive realm per se. This is seen in a variety of areas of research, including animal models of drug self-administration (e.g., see reviews by Carroll, Lynch, Roth, Morgan, & Cosgrove, 2004; Lynch, 2006; Roth, Cosgrove, & Carroll, 2004) and human laboratory studies (e.g., see reviews by Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Terner & de Wit, 2006), and is reflected in the progesterone research described in this issue. Not only have we learned that these hormones interact with neurotransmitter systems that underlie drug abuse, including dopamine (e.g., Becker & Rudick, 1999), but we have also learned that there are sex differences in drug abuse that are independent of circulating gonadal hormones, as evidenced by research on sex differences in cocaine self-administration (e.g., Hu, Crombag, Robinson, & Becker, 2004). Progress is also beginning to be made in understanding the molecular basis of sex differences in cocaine self-administration (e.g., Lynch, Kiraly, Caldarone, Picciotto, & Taylor, 2007). Further, a recent study of sexual dimorphism in gene expression reported that 13.5% of the expressed genes in the whole mouse brain are expressed differently in males and females (Yang et al., 2006), and the authors suggested that analysis by brain region may have yielded higher levels of sexual dimorphism in gene expression. Work by Dewing et al. (2006) has revealed regulation of the synthesis of dopamine by the Sry gene (testes-determining gene) located on the Y chromosome, thus indicating that some aspects of dopamine regulation are male specific. These and other recent studies are providing new justifications and new lines of investigation for exploring sex differences and how those differences may impact the current animal models of the neurobiology of addiction based predominantly on data from studies of males.

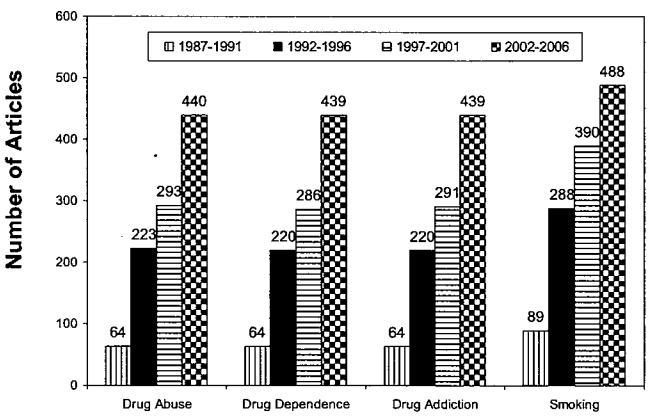

Figure 1. Number of articles cited in PubMed for the four 5-year periods from 1987–2006 based on searching on the term *gender differences* plus the terms *drug abuse*, *drug dependence*, *drug addiction*, and *smoking*.

Ironically, the early view that any male–female differences in drug abuse beyond female reproduction were likely to be of little importance coexisted with the view that drug abuse was primarily a male issue and that males were more vulnerable to drug abuse than were females, a view that was readily supported by epidemiological data showing greater prevalence of drug use and dependence among males. The irony, of course, is that if females are less vulnerable, then study of male–female differences could serve to illuminate the basis for greater male vulnerability. This view of greater male vulnerability gradually began to erode, however, with additional epidemiological data as well as data from animal research. More refined epidemiological analyses revealed that many male–female differences diminished, disappeared, or even reversed when drug use prevalence was adjusted for opportunity to use (Van Etten, Neumark, & Anthony, 1999) and when drug dependence rates were calculated only among users (Anthony, Warner, & Kessler, 1994). Recent analysis of data from the National Survey on Drug Use and Health, for example, revealed that women were three to four times more likely than men to become addicted to cocaine within 24 months of the first time they used it (O'Brien & Anthony, 2005).

Further, mounting data from drug self-administration studies in animals have failed to provide evidence of greater male vulnerability to drug abuse. These procedures have been used to study various stages of drug addiction, including initiation–acquisition, escalation, binging, and relapse. Across a variety of drugs, when researchers test for sex differences, differences are usually found and in the direction of greater female vulnerability (e.g., see reviews by Lynch, 2006; Roth et al., 2004; but see Caine et al., 2004). An exception, and perhaps more will be identified, is in the reinstatement model of drug relapse wherein females exhibit greater reinstatement than males in the drug-primed reinstatement procedure (Lynch & Carroll, 2000), and males exhibit greater reinstatement than females in the cue-induced reinstatement procedure (Fuchs, Evans, Mehta, Case, & See, 2005).

Categories of Sex–Gender Differences and Conclusion Errors

Categories of Sex–Gender Differences

Male–female differences in outcomes fall into at least three categories: (a) gender-sensitive (or sex-sensitive) outcomes, that is, outcomes are greater either in males or females; (b) gender-specific (or sex-specific) outcomes, that is, outcomes are limited to either males or females; and (c) outcomes are opposite in males and females. Numerous examples of the first two categories are readily found in the growing literature on sex–gender differences in drug abuse, and many are described in the progesterone articles in this issue. Often both of those outcomes occur in a given study.

For example, in a study of regional cerebral blood flow (rCBF), assessed by single photon emission computed tomography, in the orbitofrontal cortex (OFC) of abstinent treatment-seeking cocaine abusers, there was greater overall rCBF disturbance in males than in females (i.e., a gender-sensitive outcome), and there were gender differences with respect to the affected regions, with reduced rCBF in the right and left OFC only in males and reduced rCBF in the medial OFC only in females (i.e., gender-specific outcomes; Adinoff et al., 2006).

Reports of opposite effects in males and females, though less frequent, poignantly reveal the consequences of not analyzing data by gender. For example, in a 2.5-year longitudinal study of children with at least one parent in a methadone program, the number of changes in parental role figures had opposite effects on the risk of drug use in boys and girls, increasing the risk for girls and decreasing the risk for boys (Keller, Catalano, Haggerty, & Fleming, 2002). Had outcomes by gender not been studied, these opposite effects may have cancelled each other, thus leading to the erroneous conclusion that changes in parental role figures do not influence drug use in children. Similarly, Costello, Mustillo, Erkanli, Keeler, and Angold (2004) reported that among 730 young adults aged 19–21 living in western North Carolina, the impact of September 11, 2001, on the prevalence of substance use disorders was opposite in males and females: Rates were higher among females but lower among males. Without a gender analysis, the conclusion may have been that there was no change in substance use disorder following September 11, 2001, in that sample.

Another example of opposite effects in males and females is seen in a brain imaging study that also reported both sex-sensitive and sex-specific effects (Kilts, Gross, Ely, & Drexler, 2004). Positron emission tomography imaging of cocaine cue-induced craving revealed common areas of brain activation in males and females, including areas in which the level of activation differed in males and females. In some areas, activation only occurred in one sex. In the amygdala, opposite effects in males and females were observed: increased activation in males and decreased activation in females. Had the researchers not analyzed the data by sex, perhaps these opposite-direction effects would have cancelled each other, thus leading to the incorrect conclusion that the amygdala was unaffected by cue-induced cocaine craving. More generally, this differential pattern of activation of brain regions by cocaine cues suggests that men and women may use and crave cocaine and relapse for different reasons and that they may benefit from different relapse prevention strategies. A brain perfusion study by Tucker, Browndyke, Gottschalk, Cofrancesco, and Kosten (2004) also reported opposite effects in males and females but in different regions. Male cocaine users exhibited decreased perfusion in several brain areas (the anterior cingulate, right precentral gyrus, and right superior–medial frontal gyri), whereas female cocaine users had no areas of decreased perfusion and instead exhibited increased perfusion in the posterior cingulate. These sex differences in affected regions suggest differential relapse risk factors and differential use of pharmacological and cognitive behavioral therapies for males and females.

Conclusion Errors: A Potential Risk of Failing to Perform a Sex–Gender Analysis

These categories of sex–gender differences serve to demonstrate that failure to conduct a sex–gender data analysis carries the risk of conclusion errors. If a data set contains male–female differences but they are not detected because a sex–gender analysis is not conducted, then either of the following two conclusion errors will occur: (a) A conclusion will be drawn that an effect exists, when in fact it exists only for one sex–gender, or (b) a conclusion will be drawn that no effect exists, when, in fact, either an effect exists but only in one sex–gender or there is an effect in both males and females but in opposite directions, thus negating each other. In addition, if an effect that occurs in both sexes–genders is stronger in one than in the other but is undetected because a sex–gender analysis was not performed, then one risks failing to detect a difference in strength of an effect that could be of theoretical or clinical significance.

The Menstrual Cycle: Another Potential Source of Conclusion Errors

Not only can failure to stratify outcomes by sex–gender lead to conclusion errors, but failure to consider the menstrual cycle phase can also lead to conclusion errors. This is demonstrated in a study of cue-induced smoking craving in which the results indicated no male–female differences until stratification of data by menstrual cycle revealed that women in the follicular phase had significantly less craving than either women in the luteal phase or men (Franklin et al., 2004). These male–female and follicular–luteal phase differences are of particular importance in view of the large literature on sex–gender differences in nicotine and smoking, including women's lower cessation rates and their poorer success with nicotine replacement therapies as compared with men (e.g., Cepeda-Benito, Reynoso, & Erath, 2004). Without the menstrual cycle analysis, the conclusion that otherwise could have been drawn is that the data suggest that cue-induced smoking craving does not differ between men and women and therefore is unlikely to play a role in male–female differences reported in the literature on nicotine and smoking. Instead, the analysis of data by menstrual cycle suggests a very different conclusion, that is, that cues associated with cigarettes may play a larger role in maintaining nicotine addiction in females than in males, a conclusion that is consistent with other human laboratory data (e.g., Perkins et al., 2001). These data also could have implications for follicular phase versus luteal phase cessation quit dates for women. As described in the progesterone articles in this issue, it is this type of menstrual–estrous cycle analysis in humans and animals that initially laid the groundwork for suggesting the possibility that progesterone plays a role in the subjective effects of cocaine and then further suggested that progesterone or a progesterone-like compound may be of benefit in the treatment of cocaine addiction.

Summary and Conclusions

In the early years of NIDA-supported drug abuse research, much of the research on women was treatment related and conducted out of concern for their pregnancy status. Since then, drug abuse research on women has expanded to include females of all ages, including infants, children, and adolescents, both human and animal. This expansion has also extended to the study of male–female differences. In the early years of the expansion, reviewers in NIH study sections demanded a heavy burden of proof from drug abuse researchers who proposed to study male–female differences. The need for such research appeared not to have face validity. The tide has now changed with the growing body of literature attesting to its scientific and clinical validity. This change is reflected in the concern often expressed in study sections reviewing drug abuse grant applications that an applicant does not propose to analyze the data for sex–gender differences when in fact the literature suggests that such differences would be observed. Although this change in study section behavior has been slow, it suggests that the burden of proof is shifting from having to defend why sex–gender differences should be studied to having to defend why they should not.

In his *Scientific American* article, "His Brain, Her Brain," Larry Cahill (2005) noted that a generation of neuroscientists equates "sex differences in the brain" with mating, hormones, and the hypothalamus. Cahill (2005) turned this view upside down in his review of the widespread sex differences in brain anatomy and function and their implications for understanding brain-based disorders, including depression, schizophrenia, and drug addiction (also see Cahill, 2006). He concluded that growing numbers of researchers "... now agree that going back to assuming we can evaluate one sex and learn equally about both is no longer an option" (Cahill, 2005, p. 9). As reflected in Figure 1, many drug abuse researchers are among those numbers, including the authors of the progesterone articles in this issue. As described herein, failure to conduct a sex–gender analysis has implications beyond failure to detect male–female differences: It can lead to conclusion errors. Therefore, conducting a sex–gender analysis is not simply a matter of determining whether males and females differ in a specific outcome; instead, conducting a sex–gender analysis is a matter of conducting good science. Detection of a sex–gender difference, of course, is not necessarily an end in itself. In the case of a clinical trial, for example, finding that a treatment is effective for only males or females may have immediate application, but pursuing why it was effective in only males or females could eventually lead to better treatment for both men and women.

Figure 1 shows that there has been growing progress in the study of male–female differences in drug abuse over the past two decades. Nevertheless, much progress remains. NIH-supported human research is required to include both males and females; however, too often analysis of data by sex–gender is not conducted. And when results of sex–gender analyses are reported, too often the analyses are merely post hoc instead of resulting from empirically based or theory-driven hypotheses. Growing numbers of animal studies are examining sex differences, but the vast majority of animal studies still use only males, thus raising questions of generalizability to females. More research is needed to explore the underlying mechanisms of male–female differences in drug abuse, and more studies are needed that apply existing research findings of male–female differences to design and improve interventions. Taking these sex–gender-based approaches to drug abuse research can lead to better understanding of the etiology and consequences of drug abuse in both males and females and to better prevention and treatment strategies for both males and females.

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