

*A Review of
Clinical
Research and
Pain
Management in
Women*

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ABSTRACT

The involvement of women in clinical research has fluctuated in the course of recent medical history. Over the past fifteen years, the enactment of federal policies supporting gender-based research reflects a new appreciation of the importance of including women in clinical research. Women are increasingly participating in clinical trials for new drugs; however, gender-specific clinical data are lacking, suggesting the absence of data analysis to determine sex-related differences in the pharmacokinetics and pharmacodynamics of drugs. In this report, clinical trial data, meta-analyses, and literature reviews from the past 25 years are used to explore the barriers to in-depth clinical research on women and examine the implications of a research bias for pain management in women. While an extensive body of research on women and pain pharmaceuticals is currently being developed, there are myriad untapped opportunities for future research and policy that have the potential to supplement the knowledgebase in this area and provide critical information to clinicians and patients.

A Review of Clinical Research and Pain Management in Women

The involvement of women in clinical research has fluctuated over the course of recent medical history. Over the past fifteen years, the enactment of federal policies that support gender-based research reflects the importance of including women in clinical research. Women are increasingly participating in clinical trials for new drugs; however, gender-specific clinical data are lacking, suggesting the absence of data analysis to determine sex-related differences in the pharmacokinetics¹ and pharmacodynamics² of drugs.

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management in women. While an extensive body of research on women and pain pharmaceuticals is currently being developed, there are myriad untapped opportunities for future research and policy that have the potential to supplement the knowledgebase in this area and provide critical information to clinicians and patients.

Women and Clinical Trials

History

Over the past forty years, the role of women as subjects in clinical trials for the study of new drugs has been undervalued and their participation limited. After years of informal exclusion, the Food and Drug Administration (FDA) formally restricted the participation of women in clinical trials in 1977 (Evelyn et al. 2001). The systematic exclusion of women began in the 1960s and early 1970s, when drug companies became liable for the fetal effects of drugs such as thalidomide and diethylstilbestrol (DES), which produced physiological malformations and birth defects when taken by pregnant women (Baird, 1999). Drug companies began to limit women's participation to avoid liability; this practice of exclusion severely restricted the participation of women in drug research and laid the groundwork for future discrimination against women in clinical trials.

Women were also excluded from clinical trials because researchers were unsure of how female sex hormones might interact with the pharmacokinetics and pharmacodynamics of drugs (Kashuba and Nafziger, 1998). The fluctuation of sex hormones throughout the menstrual cycle created a challenge for researchers working within the traditional model of randomized controlled trials. Women diversified the study population and created the potential for wide-ranging drug effectiveness patterns (Britton et al. 1999). As a result, cohorts of men were used to develop new drugs, disease models, and health parameters (e.g., normal systolic and diastolic blood pressure levels). These factors contributed to a contemporary healthcare environment where information on pharmaceutical treatment protocols, dosage, and adverse effects may not be accurate for or applicable to a large segment of the population, namely, women.

By the early 1980s, the exclusion of women in clinical research gained visibility as a critical issue in healthcare. This issue resulted from the coalescence of several factors including an increase in women entering the field of medicine and scientific research, the critical realization that women had been omitted as subjects in several key research studies, and the rise of gender-specific medicine (Schiebinger, 2003). In their research on gender and the pharmacokinetics and pharmacodynamics of drugs, Thürmann and Hompesch (1998) stated, "in women, absorption, protein binding, volume of distribution, and metabolism of drugs may

differ due to hormonal influences on physiological functions.” Researchers observed the dearth of clinical information on women and cardiovascular disease, which sparked clinical investigations and media attention around the appropriateness of prevention strategies, diagnostic parameters, and treatment modalities prescribed for women. In the field of pain research, the effectiveness of analgesics was called into question when several studies elucidated the differences in the biological pain modulation systems of men and women (Gear et al. 1996; Sarton et al. 2000).

The growing body of research on sex-related differences in drug pharmacokinetics and pharmacodynamics contributed to a number of changes in policy and practice that occurred in the 1990s. At that time, both the FDA and National Institutes of Health (NIH) issued guidelines designed to reduce sex-related bias in clinical research for new drugs. In addition to creating an Office of Women’s Health Research (OWHR) and funding the Women’s Health Initiative (WHI), the NIH also enacted policy changes that required grant recipients to include representative samples of women and minorities and analyze study data by subpopulation (National Institute of Health [NIH], 1993). Similarly, between 1988 and 1998, the FDA lifted their ban on participation of women with childbearing potential and established recommendations that New Drug Applications (NDA) and Investigational New Drugs (IND) include the participation of relevant subgroups and the subsequent analysis of data to determine variability in drug response (Food and Drug Administration [FDA], 1993).

Current Status

The NIH and FDA guidelines have begun to formalize a research environment that identifies women’s participation in clinical trials as an essential component of evidence-based medicine. However, the impact of these guidelines is widely debated among researchers and clinicians, with one side claiming that a gender bias no longer exists in clinical research, and the other contending that gender bias continues in spite of the federal guidelines. Meinert et al. (2000) reviewed clinical trial reports from five prominent medical journals in 1985, 1990, and 1995 and found “no evidence of systematic bias against females.” The Center for Drug Evaluation and Research’s (CDER) report, *Women’s Participation in Clinical Trials and Gender-Related Labeling*, retrospectively reviewed 185 molecular entities approved between 1995 and 1999 and concluded that, in general, “women are participating in clinical trials of new drugs in approximate proportion to their representation in the population” (Evelyn et al. 2001). In the CDER’s review of participation by sex in clinical trials for analgesics, women tended to participate in higher numbers than men. With the exclusion of gender-specific products and participants of unspecified gender, women

comprised 62% of the study population for analgesic drug trials. However, on closer examination of the CDER data, it is apparent that women continue to be underrepresented in phase I and I/II of trials, the point at which appropriate drug dosage is often determined. Prout and Fish (2001) point out that “because most drugs fail early trials, exclusion of women from early phases may limit identification of drugs that are useful specifically for women.” In addition, Harris et al. (2000) reviewed the number of male and female participants in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute between 1965 and 1998 and concluded that, despite an increase in the number of single-sex trials including women, there have been “no substantial increases in the proportion of women enrolled in mixed-sex trials over the past 30 years.”

In addition to the inconsistent participation of women in trials, it is clear that a gender perspective is not always included in the analysis of clinical data. It is uncertain whether researchers consistently perform subgroup analysis and whether they include the results of such analysis in the drug labeling. According to the CDER report referenced earlier, “only 22% [of the products reviewed] described a gender effect” and “none recommended a change in dosing for women” (Evelyn et al. 2001). In a separate review, the FDA’s Office of Women’s Health found that “documentation with regard to sex composition and sex analysis was not consistent” and that “clinical trials were not prospectively designed to evaluate potential sex differences” (Keitt, Wagner, & Marts, 2003).

While this research reflects an overall increase in the participation of women in clinical trials, it also indicates the need for additional oversight by the NIH and FDA to ensure appropriate participation of women in all phases of the clinical trial process. The disparate research conclusions regarding the presence of a gender perspective in trials also reflects the complexity of implementing changes to the clinical trials process and the possibility of continuing barriers to the participation of women.

Barriers to Recruitment and Participation

There are several barriers to the recruitment and participation of women in clinical trials, many of which stem from characteristics inherent to the traditional research model. The need to limit liability, reduce variance, and control costs are consequences of this model that create challenges to the participation of women in clinical trials.

The 1993 FDA Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs revoked sanctions on the participation of women with childbearing potential, but did not

eliminate the exclusion of pregnant and lactating women. The liability related to potential exposure of pregnant women and their fetuses to new drugs through clinical trials warrants caution and restrictive policies; however, three-fourths of pregnant women will require medication at some point during their pregnancy (Schiebinger, 2003). Without a formal data collection method for tracking post-market information or the creation of models for extrapolating drug effects, pregnant women must resign themselves to making decisions about their health without knowing the magnitude of risk.

Clinical trial guidelines also frequently call for “blanket exclusions” of elderly participants, typically over the age of 65, 70, or 75 (Britton et al. 1999). Ideally, clinical trial subjects are free from medical conditions, comorbidities, or drug regimens that may cause variance in the research data, which explains the exclusion of the elderly, who tend to have complex medical backgrounds. However, the restriction on participation of older subjects is particularly detrimental to women, who tend to live longer than men and will most likely be consumers of new pharmaceuticals as they age. As the Baby Boomer generation reaches their sixties and as people begin to live longer due to improved medical technologies, elderly women will begin to constitute a larger subgroup within our population. It is essential that researchers re-examine the exclusion of the elderly and develop ways to respond to emerging trends in life expectancy and disease prevalence within the clinical trial model.

Exclusion of patients with multiple medical conditions from clinical trials also has an adverse effect on minority women, particularly because the prevalence of poverty in minority groups is linked to an increase in disease burden. According to Lillie-Blanton and LaViest’s 1996 study on the factors that contribute to health disparities, “there is considerable evidence that U.S. racial/ethnic minority populations experience social environmental conditions that place them at a heightened risk for ill health and injury.”

As a result of clinical trial ineligibility, there are scant data available that reflect drug effectiveness in these subgroups. The data that is available comes from the post-market surveillance information submitted by drug companies. The FDA monitors adverse event reporting through the post-market surveillance database to detect new drug effects and risk patterns related to adverse events. However, the post-market reporting process is currently voluntary within the FDA, and fraught with problems including “chronic underreporting of adverse drug reactions, occasional publicity-driven and litigation-driven episodes of over reporting and misreporting” and “variability in the quality and completeness of information...including dosage, formulation type, timing of exposure, and length of exposure and

follow-up” (Keitt et al. 2003).

Despite the advances in drug research related to the increased participation of women in clinical trials, the continued exclusion of female subgroups illuminates the inadequacy of current research methods to provide unbiased, accurate drug treatment and information to women in all demographic groups.

The cost of clinical trials may also provide a barrier to participation of women and analysis of data by sex. The use of women in clinical trials and subsequent analysis by sex increases the cost and complexity of new drug applications. It is more expensive to recruit women into trials, particularly because of the need for outreach efforts that target a diverse array of female subjects. Women hold multiple roles within our society; as a result, successful recruitment of women into trials involves a combination of traditional and non-traditional enrollment practices. According to a University of California at San Francisco study on the challenges of recruitment of women into clinical trials, “while the [NIH] requirements preclude the use of cost as a reason for excluding women and/or minorities, the additional funding necessary to recruit adequate numbers of study participants has not been provided” (Brown, Long, Weitz, & Milliken, 2000).

The FDA recommendation that study data be analyzed by sex also contributes to the increased cost of clinical trials. In order to examine subgroup effects, researchers must recruit enough study subjects in each subgroup to perform a power analysis. Once the trials are conducted, additional resources are expended on data analysis. Significant outcomes must be subsequently incorporated into the new drug application, medication labeling, and consumer information. The increased cost of including women in trials, coupled with the voluntary nature of the guidelines established by the FDA may prohibit some researchers from seeking out female research subjects or performing data analysis based on sex.

Additional Barriers to Research

The implementation of the Health Information Portability and Accountability Act (HIPAA), federal legislation designed to increase the confidentiality of patient information, inadvertently created a barrier to accessing health information from medical records for research purposes. Although HIPAA was not intended to inhibit research, the implementation of its privacy clause eliminated access to medical records without specific informed consent from the patient (O’Herrin, Fost, & Kudsk, 2004). Prior to HIPAA, researchers could construct a retrospective study and use data mining techniques to extract relevant information from patient records. This method allowed

researchers to study the effects of a particular drug on women who may not have participated in prospective trials; for example, on pregnant women, or women with multiple diseases. While retrospective studies may not be as precise as randomized controlled trials, they do provide some insight into the potential risks and benefits of drug treatments and may serve to supplement the drug information currently available to women. However, the enforcement of HIPAA makes such retrospective studies unlikely until sufficient numbers of potential study subjects can give consent for research into their medical records.

Developing research studies that include a gender perspective involves multiple challenges. Consequently, policies designed to eliminate bias in clinical research should identify the barriers to a gender-based approach, such as cost and complexity of trials, and create an environment that supports novel approaches to clinical research.

Women and Pain

The next section will explore the sex-related differences in the pain experience and discuss how the sex bias in clinical research has had a negative impact on the management of pain in women.

Women are more likely than men to experience recurrent pain and to receive treatment through the healthcare system (Unruh, 1996). Unruh also noted that headache, abdominal pain, facial or temporomandibular joint (TMJ) pain, and musculoskeletal pain are more common and more severe in women than in men. Over the past several years, researchers have begun to examine pain in men and women and have found significant differences in women's physiological and psychological perception of pain, the treatment methods for women with pain, and women's response to pain medications.

Sex-related differences in the pain experience

Research on pain over the past twenty years suggests that differences in women's experience of pain, compared with that of men, can be attributed to biological and physiological differences (Zubieta et al. 2002; Gear et al. 1996), and psychological factors (Campbell, Clauw, & Keefe, 2003).

When women are exposed to painful stimuli, whether in a clinical or experimental setting, their physiological response differs from that of men. Women have a greater sensitivity to pain that is induced through pressure, thermal, electrical, or ischemic stimuli (Fillingim & Maxiner, 1995). Zubieta et al. (2002) used positron emission tomography (PET) to detect pain modulation in men and women through the activation of the μ -opioid system. Their study found that "at matched levels of pain intensity, men and women...differ in the magnitude and direction of

response of the μ -opioid system in distinct brain nuclei.” Both men and women are able to attenuate pain through the μ -opioid system; however, the degree of response differs.

Research on other pain modulation systems in the brain, such as the k-opioid receptors, amplifies this sex-related difference. The k-opioid system appears to more effectively modulate pain in women than in men. Over the course of several studies, Gear et al. (1996, 1999, 2003a, 2003b) identified the sex-related differences inherent in the k-opioid system, including the proficiency of the k-opioid system in modulating pain in female subjects. Gear et al. (2003a) were also able to demonstrate that low doses of k-opioid agonist drugs (e.g., nalbuphine) actually increased pain levels in men, indicating that the effectiveness of different classes of pain drugs may vary based on the sex of the patient.

Researchers have also identified two endogenous analgesic systems that are specific to women, pregnancy-induced analgesia (PIA) and vaginocervical stimulation-produced analgesia (VSPA) (Fillingim & Ness, 2000). Each of these systems has a unique set of stimuli that activate an increase in the pain threshold of women. PIA is detectable throughout pregnancy, with an analgesic peak just prior to birth (Cogan & Spinnato, 1986), while VSPA has been shown to increase mechanical pain tolerance during direct stimulation (Whipple & Komisaruk, 1985).

The series of biological differences in women’s perception of pain indicate that traditional protocols for pain management used in clinical settings (e.g., type of drug, formulation, and dosage) may not be appropriate for all women. The issue of pain management and the pharmaceutical treatment of pain in women will be discussed in the next section.

Psychological factors that may affect pain perception in women include depression, self-esteem, perceived stressors, and coping mechanisms. Depression as a comorbidity of pain is more likely to occur in women than in men (Meana, 1998), and women with chronic, painful illness are more likely to suffer from depression (Campbell et al., 2003). It is interesting to note that women who are being treated for depression and/or for a chronic illness are likely to be seen as poor candidates for clinical research, and may be excluded from clinical trials because of their complex medical history

In the absence of clinical trials for pain that include women or the analysis of data for sex differences, the various dynamics that influence the pain experience in women cannot be explored and appropriately integrated into pain management plans for women. In addition, there is little research on the sex-related differences in the prevalence or

experience of acute pain. In order to fully address the needs of patients, research on all types of pain must address the sex-related issues in diagnosis, treatment, and follow-up.

The management of pain in women

Women with pain, typically severe or chronic pain, access the healthcare system more frequently than men (Unruh, 1996). Once in the healthcare system, women and men are treated very differently with respect to pain management. In 1994, Cleeland et al. found that women were less likely to receive adequate analgesia for relief of their cancer-related pain. Patients from minority groups were also less likely to receive adequate pain relief, putting female minorities at high risk for inappropriate pain management. Cleeland suggests that several factors may contribute to the variability in pain management among patients, including “inadequate dose of an analgesic drug of the appropriate potency...[or] discrepancy between the physician’s and patient’s estimate of the severity of the patient’s pain.” Additional evidence suggests that physicians may perceive women as being “overanxious” about their pain when compared with men, leading to a biased pain assessment and inadequate care (American Medical Association, 1991). These data indicate that the lack of clinical research on effective pain management in women has resulted in the unsuccessful treatment of women’s pain.

In order to properly manage women’s pain, clinicians need to be aware of any sex-related differences in the drugs they prescribe. For example, the first-pass clearance rate, a measure of how much drug is inactivated by the liver before it can produce its effect in the body, differs between men and women. Acetaminophen, a drug commonly used in pain medication, is eliminated from the body by women at 60% of the rate it is eliminated by men (Merkatz et al. 1993). When men and women are prescribed similar doses of acetaminophen, women are at higher risk for hepatotoxicity related to chronic overdose.

Women in different stages of the menstrual cycle or life cycle (e.g., menopause, pregnancy), as well as women taking oral contraceptives, have different rates of drug metabolism, clearance, and pharmacologic response (Anthony & Berg, 2002). Women taking oral contraceptives have higher clearance rates of the pain relieving drugs acetaminophen, morphine (Anthony & Berg, 2002), and paracetamol (Thürmann & Hompesch, 1998). Ideally, clinicians should be able to cross-reference a patient’s menstrual status with a particular drug to determine its clinical efficacy and appropriateness of dosing.

Recent research by Margaret Miller (2001) supports the idea of sex-related differences in drug pharmacokinetics and pharmacodynamics, particularly in the areas of drug toxicity and adverse events. While men

and women report the same number of adverse events related to a pharmaceutical regimen, the events reported for women tend to be more serious. Eight of the ten drugs withdrawn from the market by the FDA since 1997 generated greater health risks for women than for men (General Accounting Office, 2001). In the area of pain management, women receiving opioid analgesics, e.g., morphine, experience respiratory depression and other adverse effects more frequently than men (Pleym, Spigset, Kharasch, & Dale, 2003). Schwartz (1999) states that “since the μ -receptor opioids [i.e., morphine-like opioids] produce more nausea, sedation, confusion, constipation, and respiratory depression than the κ -opioids, there may be clinical advantages to greater use of the κ -opioids in women,” suggesting that sex-targeted prescribing methods for analgesics may be used to improve efficacy and decrease the risk of adverse effects in women.

The historical exclusion of women in clinical trials and the absence of trial data that are analyzed for sex and life cycle differences have resulted in a lack of data to support enhanced prescribing methods for women. Clinicians lack adequate sex-specific drug information and continue to prescribe drugs for pain management that have not been evaluated in rigorous trials for their effects in women. As a result, women are at risk for variable pain relief, unknown adverse effects, and suboptimal care.

Research and Policy Implications

The changes in FDA and NIH policy regarding clinical trials and women have done a great deal to bring the issue of gender bias in clinical trials to the fore and have begun to foster a research environment where the exploration of individual or subgroup variation is identified as a critical part of clinical research. While an extensive body of research on women and pain pharmaceuticals is currently being developed, there are myriad untapped opportunities for future research and policy that have the potential to supplement the knowledgebase in this area and provide critical information to clinicians and patients.

Research

Research on new drugs should continue to use representative samples of women, including relevant subgroups of women. Researchers should collect information from female subjects regarding menstrual cycle and life phase and use this information when performing their sex-related analysis of drug effectiveness, adverse events, and dosage. In addition, a diverse group of healthy women should be recruited more heavily into phase I and I/II trials in order to gauge early drug effects and calibrate appropriate dose levels for women in various demographic groups.

For women who have a disease or condition that prohibits them from participating in a trial, post market surveillance is the only option for clinical data collection. The FDA needs to evaluate and standardize the method of data submission for approved drugs, particularly related to subgroups that were excluded from the clinical trials, so that post-market information accurately reflects the drug risk profile in a clinical setting.

Finally, the trend in research towards pharmacogenomics, the development of individualized therapies based on the genetic composition of the patient, has the potential to improve pharmaceutical therapy by linking drug effectiveness or toxicity patterns to genetic profiles within populations (McLeod & Evans, 2001). However, the value of pharmacogenomics hinges upon the inclusion of women in studies that seek to identify potential genetic targets for drugs.

Funding

In order to facilitate the development of drug-related data, the funding for clinical trials should reflect the change in complexity of trials that include women. Differential funding should be made available to offset the cost of recruiting women, particularly minority women, which may require more recruiters and various recruitment sites. Additional funding may also be useful for compensating women's participation and increasing retention. Brown et al. (2000) found that women's compensation for clinical research may be inadequate in exchange for their participation. As primary caregivers within the home, women may require additional compensation to cover the cost of childcare or eldercare during study participation. Finally, the additional research costs resulting from subgroup data analysis and the need for long-term follow-up and reporting of drug effects on women may also warrant differential funding patterns for research studies.

Prospective Recruitment of Women into Clinical Trials

In order to offset the effects of HIPAA on data mining for clinical research, health systems are developing prospective clinical trial recruiting systems that review women's medical profiles for eligibility in new studies. Researchers can input study criteria into the registry, which generates a list of potential subjects. The University of Michigan Health System enrolled over a thousand women into its research registry through recruitment within the community and at the point of care using targeted media campaigns. Women were educated about the opportunities and benefits of clinical trial participation, and entered into the database after giving informed consent (Rogers, 2002). Federal support and funding is necessary in order to expand upon the success of research registries in recruiting women into clinical trials.

Education

Education is a key component of healthcare because it initiates discussion and understanding of information that impacts the way care is provided. The historical exclusion of women from clinical trials has disabled the process of information sharing within healthcare by limiting the availability and downplaying the relevancy of sex-specific information. It is essential that pharmacists, nurses, and doctors integrate new sex-specific drug information as it becomes available through clinical research. Healthcare systems should facilitate this process by providing access to research databases, posting critical drug information updates, and developing clinician education campaigns that share emerging data that may impact the provision of care to both men and women. Healthcare systems are also in a position to collect and review hospital- or clinic-specific data to identify any gender-related differences in evaluating and treating clinical conditions, such as pain. Finally, female patients and their families need information about the potential sex-related risk factors that may result from a particular drug regimen. The database of drug-specific effects in women is limited; however, women should be given general information on how sex hormones and female biology have the potential to impact the effectiveness of drugs.

Conclusion

A considerable amount of research demonstrates the importance of using gender-based information when treating pain in women. It is crucial that scientific research continue to support the exploration of sex-related differences in physiology, disease pathology, and the pharmacokinetics and pharmacodynamics of drugs so that women and their care providers can access accurate information and make informed health choices.

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Footnotes

Pharmacokinetics is the process in which drugs are taken up by the body and subsequently transformed, distributed, metabolized, and eliminated from the body (Biotech Life Science Dictionary, 2004).

Pharmacodynamics is the study of the biological effects of drugs in the body (Biotech Life Science Dictionary, 2004).