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Sex Differences in Long-term Opioid Use:

Cautionary Notes for Prescribing in Women

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Opioid therapy for chronic noncancer pain has been the topic of debate, including who is an appropriate candidate for prescription, what are correct dosages, and how to prevent opioid-related accidental death. One overlooked aspect of this debate is attention to the sex differences related to the use of opioids and the specific risks for women. Epidemiological studies of pharmacy claims in the United States show that opioids are more likely to be prescribed to women than men and that women are more likely to be taking higher doses of opioids.¹ In recent years, opioid prescription has increased among both sexes, but the temporal slope for opioid prescription is greater for women than for men, suggesting that this sex disparity is widening over time.²

Women are at greater risk for acquiring varied chronic pain conditions, and women on average experience greater pain intensity than men. For these reasons, women are at greater risk for the varied iatrogenic consequences of opioid prescription. Also, women are at greater risk for opioid misprescription: the prescribing of opioids for pain conditions such as fibromyalgia, headache, or osteoarthritis, with efficacy data suggesting that opioid therapy is nonbeneficial.

While both men and women are at risk for opioid-induced endocrinopathy,³ several studies have documented that women-specific risks include amenorrhea and infertility in reproductive-aged women and reduced sex steroids in postmenopausal women.⁴ Hormonal imbalance is associated with increased pain intensity and with the development of secondary complications, such as impaired stress and immune responses.

Regarding opioid use in pregnancy, an epidemiological case-controlled study conducted by the Centers for Disease Control and Prevention showed that maternal opioid exposure significantly predicted infant conoventricular septal defect, atrioventricular septal defect, atrial septal defect, hypoplastic left heart syndrome, tetralogy of Fallot, and pulmonary valve stenosis; other risks included spina bifida and gastroschisis.⁵ The study excluded women who reported illicit opioid use; therefore, the findings are relevant to female pain patients who are considering pregnancy. Studies describing specific risks of opioid exposure in infants of mothers who are using opioids for nonobstetric chronic noncancer pain are lacking; thus, infant safety has not been established. Findings from the acute pain literature

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suggest that there are likely to be risks in breastfeeding mothers who are using opioids on a long-term basis. If long-term opioid use cannot be avoided in a breastfeeding mother, the risks may be minimized by providing safety instructions regarding monitoring for warning signs of toxic effects in infants.

Among chronic pain clinic patients who are taking opioids, women are more likely than men to have polypharmacy.⁶ Such pharmaceutical complexity places women at greater risk than men for drug-drug interactions, additive adverse effects, and potential for poisoning or overdose. Rates of toxic reactions have tripled among women since 1999, and opioid-related poisoning hospitalizations have increased for women but not for men. Examples of factors related to poisoning could include overprescription, overuse by the patient, adverse effects, or toxic reactions related to drug-drug interactions. A study of unintentional pharmaceutical overdose fatalities reported that prescribed opioids were present in 44% of women.⁷ Drug monitoring program records showed that among fatality cases, women were more than twice as likely as men to have received prescriptions from 5 clinicians or more in the prior year.⁷ Therefore, women are at greater risk for polypharmacy, for unintentional poisoning death, and for receiving multiple opioid prescriptions from multiple providers.

Psychosocial factors profoundly influence the experience of pain and coping with pain. Women are more likely than men to have depression and anxiety, 2 factors that strongly predict the receipt of opioids. Interpersonal factors are emerging as influential for opioid prescription and level of use. For instance, women with solicitous spouses are more likely to use greater amounts of opioids; the same is not true for men with solicitous spouses. Physician prescribing patterns have been linked to patients' in-office display of pain behaviors,⁸ but data do not suggest sex differences. Finally, women are significantly more likely than men to endorse having poor capacity to set limits with others, and they are also more likely to report that their fear of disappointing others leads them to make poor decisions about their pain care. For instance, women are much more likely than men to exhibit poor pacing and to push themselves into greater pain severity in an effort to maintain their role in the family. Furthermore, women are more likely than men to endorse a lenient attitude toward taking pain medication to treat the consequences of poor pacing and poor self-care.⁹

Among persons seeking treatment for opioid abuse, women are more likely than men to report having received their opioids in the form of a legitimate prescription.¹⁰ As such, physicians may have a greater opportunity to prevent the misuse of opioids by women. Sex-specific risks include endocrinopathy, infertility, polypharmacy, unintentional poisoning, and abuse; these factors should influence decision making regarding initiating or continuing opioid therapy. Sex-specific monitoring in women who are taking opioids includes ongoing assessment for pregnancy plans, endocrinopathy, physician shopping, and the use of opioids to medicate psychosocial factors. Before initiating opioid treatment for chronic pain, in women or men, prescribers should fully assess the individual risks and benefits of the therapy and have a thorough discussion of the goals, risks, and consequences of such therapy with each patient.

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