Women and the opioid crisis: historical context and public health solutions

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Driven by a legitimate but overly opioid-focused response to pain, the United States is currently experiencing an opioid crisis, a crisis with parallels to the first opioid epidemic at the turn of the 20th century. Women, particularly white reproductive-age women, are increasingly the face of the opioid crisis. Given the penetration of opioid misuse and addiction across all income and insurance strata, any provider who cares for women needs to be prepared to assess and evaluate opioid use, misuse, and addiction. Although responsible opioid prescribing is essential, treatment capacity must be expanded and be inclusive of the unique needs of women. However, the public and public health response to the opioid crisis must include rolling back the war on drugs. The continued criminalization of the public health issue of drug use and the medical condition of addiction is unethical, ineffective, and inhumane. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

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Opioids have been part of human culture and medical practice for millennia. Addiction to opioids, however, is a far more recent development. The first opioid epidemic was concentrated in Western Europe and the United States around the turn of the 20th century. Women, primarily white upper- and upper middle-class women, were prescribed opioids by physicians for the treatment of "female ailments," such as dysmenorrhea and "hysteria." Opioid formulations were widely available as so-called "patent medicines," almost all of which were explicitly marketed to women and children. Alcohol, consumed primarily in public spaces, such as saloons, was the province of men, and opioids became the province of women. It is estimated that the opioid supply could have supported a maximum of 4.59 opioid-addicted individuals per 1,000 persons (1), two-thirds of whom were women (2).

The U.S. is experiencing at least its third opioid epidemic. With only 4.6% of the world's population, the U.S. consumes more than 80% of the global opioid supply (3) and estimates of opioid misuse approach 4.7% of the population (4). The current opioid epidemic bears strong parallels to the first. Not only is it driven by opioid prescribing and is thus iatrogenic in origin, but also as before, women figure prominently in this epidemic.

Women bear a larger behavioral health burden than men and are more likely to report past year serious psychologic distress as well as any mental illness including a major depressive episode, anxiety disorder, and post-traumatic stress (5). Women have a higher prevalence of adverse childhood experiences, such as physical or sexual abuse (6), and are more likely to experience gender-based violence as adults (6, 7). Women are more likely to report pain (especially category 3 or 4 pain) than men (8), owing to both their reproductive capacity (for example dysmenorrhea and endometriosis) as well as to a greater prevalence of painful chronic conditions (such as arthritis and fibromyalgia) (7, 9). Consequently, women of reproductive age receive more prescription medications than men (10), particularly for psychotherapeutic medications including opioids (4). Women also have a greater prevalence of longer-term opioid medication use (11). Almost 40% of women aged 15–44 years report receiving at least one opioid prescription in 2015. Of the 2.1 million initiators of opioid misuse per year, 1.2 million (57%) are women, which translates to 3,300 women per day initiating opioid misuse in the U.S. (12).

Women have greater health care utilization than men (13) and more

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physician visits not inclusive of maternity care (14). However, providers are less likely to assess women for substance use and misuse and tend to miss signs of addiction in women (15). Even within an implementation trial of Screening, Brief Intervention, and Referral to Treatment (SBIRT) women were less likely to be screened for alcohol and, among those who screened positive, even less likely to receive a brief intervention or referral to treatment (16). This may be due to the fact that providers do not associate substance use, misuse, and addiction with women, much less with white insured women.

Although more men die from opioid overdose in the U.S., the rate of death is increasing more rapidly for women than men. From 1999 to 2010, prescription opioid overdose deaths increased 400% for women and 237% for men (17). Since 2007, more women have died from drug overdoses than from motor vehicle crashes (18). In 2015, the last year for which complete data are available, opioid-related overdose (18) took the lives of 31 women per day.

Because opioid prescribing has perhaps peaked and leveled off (19, 20), the epidemic is shifting to heroin (21). Heroin use is increasing most rapidly among women, individuals 18–25 years of age, and non-Hispanic whites (22). Whereas <20% of individuals who initiated heroin use in the 1960s were women, today >50% of heroin use initiators are women (23). Among women who used heroin during the previous year, 7 out of 10 reported also misusing prescription opioids, and overall ≥75% of heroin use initiators began their opioid use with a prescription (24). Interestingly, heroin use has increased similarly across all income strata and more among women with private insurance than among those with Medicaid (22). This trend is likely to continue as heroin prices fall and it becomes increasingly available in places where it had been unknown (25).

Just as who a heroin user is has changed, so has heroin. Since 2013 there has been a sharp increase in heroin seizures testing positive for fentanyl, especially east of the Mississippi (26). Fentanyl is a synthetic opioid 50–100 times more potent than morphine or heroin. Often illicitly manufactured, it is mixed into the heroin stream or sold as counterfeit pills and has contributed greatly to the continued increase in overdose deaths (27).

The opioid crisis, particularly the increase in overdose deaths, has led to a measurable rise in mortality rates especially among non-Hispanic whites in midlife (28). This reverses the long-term decline in mortality rates in the U.S. and is in stark contrast to the continuing falling mortality rates in the rest of the developed world. This mortality reversal resembles the AIDS epidemic, which took the lives of 650,000 individuals in the U.S., but perhaps with less public awareness (28). Mortality rates are higher in rural than in urban areas, and, in rural areas, highest among women (29).

PAIN, THE FIFTH VITAL SIGN

The current opioid crisis arose from changes in opioid-prescribing practices that began in the 1990s (1). In response to a recognition that pain was undertreated, untreated pain led to chronic pain, and chronic pain was costly, common, and interfered significantly with quality of life, a movement arose to make pain more "visible" in clinical care (30). The "Fifth Vital Sign" was first introduced by the American Pain Society in 1995 (31) and became a Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations) standard in 2000. The uptake of the 10-point scale coupled with a growing emphasis on overall patient satisfaction led to a remarkable increase in opioid prescribing. Sales of prescription opioids quadrupled from 1999 to 2012 (32) with no change in the self-report of pain (33, 34).

Opioid prescription for the management of chronic pain rested on a series of assumptions: opioid addiction was rare in pain patients; opioids were safe and effective for chronic pain; and opioid therapy could easily be discontinued. Although the evidence supporting these assumptions was thin at best, these talking points were widely disseminated, in particular by Purdue Pharma (the manufacturer of Oxycontin). From 1996 to 2002, Purdue Pharma funded more than 20,000 pain-related educational programs and pursued an aggressive marketing campaign directed at physicians to increase opioid prescribing (35). Additionally they provided financial support to the American Pain Society, the American Academy of Pain Medicine, the Joint Commission, and the Federation of State Medical Boards, which issued guidance to protect physicians from adverse outcomes associated with opioid prescribing (36). With an annual revenue of 3 billion dollars, mostly from Oxycontin, the Sackler family, which owns all of Purdue Pharma, became the "newcomer" to the Forbes 2015 list of richest U.S. families (37).

The evidence to support the assumption that opioid addiction was rare in pain patients came from a 111-word letter to the editor published in the *New England Journal of Medicine* in 1980. The authors describe a review of almost 40,000 medical records, of whom almost 11,882 received at least one opioid prescription, with only four cases of "reasonably well documented addiction" (38). To date, this letter has been cited 959 times (39). The evidence to support functional improvement for individuals with chronic pain, which was commonly cited in the 1990s, is of slightly better quality. Reporting a case series of 38 individuals treated with opioids for nonmalignant pain, Portenoy and Foley concluded that "opioid maintenance therapy initiated for the treatment of chronic nonmalignant pain can be safely and often effectively continued for long periods of time"—a conclusion that stands in contrast to the data, because only 11 individuals (29%) reported adequate pain relief and there were no measurable improvements in social function or employment (40).

Contemporary meta-analyses and systematic reviews support neither the safety nor the efficacy of opioids for the treatment of pain. In a review of 38 studies, rates of misuse averaged 21%–29% (95% confidence interval [CI] 13%–38%) and rates of addiction 8%–12% (95% CI 3%–17%) (41). Meta-analysis comparing the efficacy of different opioids demonstrated a nonsignificant reduction in pain from baseline in the short term and no evidence regarding long-term (>16 weeks) efficacy (42). Even the American Pain Society's "Guideline for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain" similarly commented on the absence of long-term data. Compared with placebo,