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Commentary

The Non-Symmetric Axiom XX ≠ XY of the Opioid Crisis

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Abstract

Clinicians are taught to rely on a set of logical axioms when they select a pharmaceutical product to prescribe to include opioid agents. Prescribers may be influenced to prescribe a product by promotion and marketing of that product by its sales representative. The first wave of the opioid crisis has been identified in 1991 when deaths caused by the use of prescription opioids and opioid combinations began to rise sharply due to an increase in the prescriptions for the treatment of pain. Relative historical and present epidemiology, and current pharmacokinetic and pharmacodynamic data differences between genders may have been overlooked, ignored, or may have gone unnoticed when the manufactures, prescribers, and dispensers assessed the opioid risks among women. The central theme of this report is to highlight the data related to known sex and gender differences of opioid pharmacology, opioid adverse effects, opioid misuse, and the development of opioid use disorder to argue that women are an "at risk population" when opioids are prescribed to them, and that this data was available but not utilized by stakeholders. First, both the epidemiology centered on pain prevalence and the rate of opioid use as it pertains to females will be compared with comparable data for males. Second, historical data centered on opioid use and misuse specific to females to accentuate the observed differences with males. Finally, gender and sex differences in opioid-mediated analgesia and opioid fate in humans will be presented.

Introduction

An axiom is a statement that is a well-established or so evident that it is accepted without controversy or question. An axiom used in a logical approach is simply a foundation or starting point for reasoning. Mathematical axioms are statements that are assumed to be true. There are five basic axioms of algebra [1]. The types of axioms are the reflexive axiom, symmetric axiom, transitive axiom, additive axiom, and multiplicative axiom. The second algebraic axiom is the "Symmetric Axiom" where numbers are symmetric around the equals sign: If a=b then b=a. A logical axiom can be considered a rule of inference that happens to have no background. Clinicians are taught and rely on a set of logical axioms when they select a medicinal or pharmaceutical product to prescribe. This includes opioid agents. These axioms are based on primary literature sources, which include peer-reviewed randomized, double-blind clinical trials that compare medications. Also, clinicians may use secondary literature sources that should include "drug facts and comparisons," "the medical letter on drugs and therapeutics" and review articles in peer-reviewed journals that compare drug classes and offer recommendations about drug choices. Finally, clinicians may be influenced to prescribe a particular product by promotion and marketing of that product by its sales representative. Kornfield et al. published their 2013 review of the promotion of prescription drugs to consumers and providers between 2001 and 2010 [2]. These authors concluded that during this period the manufacturers of branded pharmaceuticals, which included Oxycontin®, continued to expend considerable sums on promotion to influence both consumers and providers. Kornfield et al. [2] Schwartz and Woloshin published data centered on medical marketing in the United States for the period 1997-2016 [3]. These authors found spending on medical marketing of drugs, disease awareness campaigns, health services, and laboratory testing increased from $17.7 to $29.9 billion. Schwartz LM, et al. [3] Further, direct to consumer advertising for prescription drugs and health services increased substantially. They concluded that despite the increase in the marketing effort over 20 years, regulatory oversight remains limited. Schwartz LM, et al. [3] Van Zee using "Oxycontin® Marketing Plans from 1996-2001" presented a valid argument that the manufacturer of OxyContin® pursued an ''aggressive'' campaign to promote the use of opioids emphasizing the greater benefits of their product as compared to other products without disclosing the risks [4].

Madsen et al. reported the results of their cross-sectional survey of American College of Obstetricians and fellows to determine the opioid prescribing knowledge of its fellows [5]. The results of this survey led them to the conclusion that the obstetricians and gynecologists prescribed a median number of 26 opioid pills per patient for indications that included post-surgery pain, pain due to vaginal birth, ovarian cysts, endometriosis, and chronic pelvic pain. Madsen et al. [5] Further, regarding knowledge of opioid misuse, 81% incorrectly identified the main source of diversion was from friends or family members and that 44% did not know how to properly dispose of unused prescribed opioid. Madsen et al. [5] Moreover, Ellenbogen and Segal published their findings from the examination of the differences in prescribing of opioids among general physicians, nurse practitioners, and physician assistants. They used serial cross-sectional analysis of prescription claims from 2013 to 2016 from publicly available data with the Centers for Medicare and Medicaid Services. Ellenbogen MI, et al. [6] These authors discovered relatively extremely high rates of opioid prescribing among nurse practitioners, and physician assistants. Ellenbogen MI, et al. [6] One factor that may explain this high rate of prescribing opioids by midlevel providers may be explained by a recent news account that reports that Purdue Pharma told sale representatives: "that midlevel providers are critical to our success" and referred to them as "high-value Oxycontin® prescribers" in a 2015-2016 training session. Nelson KL, et al. [7] Nguyen et al. analyzed Medicare part D prescription data from 2014 to 2016 to study the influence of pharmaceutical payments on physicians. Nguyen TD, et al. [8] They discovered that prescribers who received opioid-specific payments prescribed 8784 opioid daily doses per year, which were higher than their peers who did not receive any such payments. Hydrocodone-related payments resulted in 5161 additional daily doses of hydrocodone, oxycodone-related payments caused 3624 additional daily doses of oxycodone and fentanyl-specific payments resulted in 1124 daily doses being prescribed per year more than those prescribed by the physicians who did not receive incentive payments. Nguyen TD, et al. [8] Among 63,062 physicians who received opioid-specific payments a 1% increase in the amount of payments was associated with 50 daily doses of opioid. Nguyen TD, et al. [8] These authors reached the conclusion that physicians who receive direct payments from opioid companies tended to prescribe substantially larger quantities, particularly of hydrocodone and oxycodone. Nguyen TD, et al. [8] It has been acknowledged that the opioid epidemic is considered to have occurred in three waves. The first wave has been identified to have occurred in 1991 when deaths caused by the use of opioids began to rise sharply due to an increase in the prescriptions of medications containing opioids and opioid combinations for the treatment of pain. Smith RG, et al. [9] This increase in the prescriptions was influenced by reassurances from pharmaceutical companies and medical societies that the risk of addiction to prescription opioids was very low. Smith RG, et al. [9] Over the last few years, Purdue Pharma has faced roughly 2,000 lawsuits over the promotion and advertising of Oxycotin®.

Purdue Pharma has denied the allegations that they contributed to the opioid crisis and further averred that heroin and fentanyl are more responsible than painkillers and that the U.S. Food and Drug Administration approved label bears a warning about the risks of using opioid. Quigley A, et al. [10] This prevailing point of view is reminiscent of the 19th century view that opiate addiction was a bad habit indulged in by weak-willed people. A proven resolve is that the U.S. Food and Drug Administration approved label warnings about the risks involving opioid use is sufficient to prevent unnecessary prescription of these drugs. Relative historical and present epidemiology, and current pharmacokinetic and pharmacodynamic data differences between genders may have been overlooked, ignored, or may have gone unnoticed when the manufactures, prescribers, and dispensers assessed the opioid risks among women. The central theme of this commentary is to highlight the data related to known sex and gender differences of opioid pharmacology, opioid adverse effects, opioid misuse, and the development of opioid use disorder to argue that women are an "at risk population" when opioids are prescribed to them, and that this data was available but not utilized by stakeholders. First, both the epidemiology centered on pain prevalence and the rate of opioid use as it pertains to females will be compared with comparable data for males. Second, historical data centered on opioid use and misuse specific to females to accentuate the observed differences with males. Finally, gender and sex differences in opioid-mediated analgesia and opioid fate in humans will be presented.

Pain Prevalence

A number of regional and large-scale epidemiological studies reveal that pain is reported more frequently by women than men. Fillingim RB, et al. [11] The Z-scores, lower Z-scores representing higher pain sensitivities, showed that the above-noted difference was statistically significant ($P<0.05$) for all pain measures. Fillingim RB, et al. [11] Mogil and Bailey claim that women suffer chronic pain and disability more frequently than men and are more likely to be prescribed opioids [12]. Further, Pieretti et al. declare that women report more severe levels of pain, more frequent episodes of pain, pain in more varied areas of their bodies, and pain of longer duration than men [13]. Moreover, they explain that biological factors, specifically the differences in sex hormones, are thought to be the main cause for this sex difference in pain perception and the greater prevalence of chronic pain among females. Pieretti S, et al. [13] Craft and Smith et al. claim that estradiol and progesterone show complex pronociceptive and anti-nociceptive effects on pain sensitivity of a protective nature, [14] especially when examining the association between the decreased androgen concentrations and chronic pain. Smith YR, et al. [15] These assertions are validated by Owens' research and emphasized by Terplan

[16,17]. Data from the National Health and Nutrition Examination Survey from 1999 to 2012 reveal that women are more likely to be prescribed opioid analgesics.

Frenk SM, et al. [18] Anthony et al. analyzed the gender differences in the most commonly prescribed medications dispensed from a national drugstore chain during 2002-2003 and found that females of reproductive age received a greater number analgesics and specifically propoxyphene with acetaminophen as compared to men [19]. Given, that females are statistically more likely be prescribed opioids and for put on longer-term opioid medication, they run a greater risk of becoming addicted more rapidly than men. Terplan M, et al. Becker JB, et al. [17,20] Lerescsch has reported that there exists a gender-dependent difference in pain treatment influenced by both patient's and provider's characteristics. Leresche L, et al. [21] A summary report authored by Van Houten et al. present data from the United States for the period 1999–2017 and describe the changes in the ages in drug-specific overdose death rates to include both prescription opioids, synthetic opioids, and heroin. VanHouten JP, et al. [22] During this period, the crude rate of drug overdose deaths among women aged 30-64 years in the United States increased by 260%; synthetic opioids and heroin-related deaths in the same population increased by (1,643%) and (915%), respectively. Finally, [22] Van Houten, et al. concluded that the increase in drug-related mortality may be caused by increases in certain drug combinations that include antidepressants, benzodiazepines, cocaine, and opioids [22].

Historical Data

In the 19th century, opiates were prescribed or dispensed to treat a wide variety of conditions: hiccoughs, neuralgias, alcoholism, respiratory conditions, malaria, syphilis, insomnia, and anxiety. Kendall SR, et al. [23] A review of medical journal articles and addiction centered secondary medical literature sources recount that paregoric, laudanum, or opium compounded drugs were specifically marketed, prescribed, and dispensed to treat painful menstruation and nervous disability. Kendall SR, et al. Raketić D, et al. Courtwright DT, et al. Courtwright DT, et al. [23-26] Kendall recounts that, throughout history, substance addiction among females has been largely the result of inappropriate overmedication practiced by physicians and pharmacists, media manipulation, or the patients themselves in an attempt to cope with internal and external stresses of life [23]. Raketić et al. [24] have reported that the prevalence of opiate addiction among women has been recorded since as early as the beginning of the 19th century. Raketić et al. [24] Moreover, these authors claim that opioid addiction among women developed during adolescence and was mostly an unwanted iatrogenic effect of compassionate treatment approaches. Raketić et al. [24] Courtwright recounts that the dominant type of morphine and opium addicts were described as white, middle-aged, middle class or upper-class females whose addiction, in the majority of cases, was iatrogenic in origin. Courtwright DT, et al. [25] By the 1940s, the opioid addict profile changed and came to be defined as a young, lower-class male who abused heroin for nonmedical use. Courtwright DT, et al. [25] Using United States residential clinic attendance data for 1860-1920, Courtwright further reported that southern whites had the highest opiate addiction rates in the country or even in the world. Further, [26] Courtwright claimed that, in the mid-19th century the popularity of opiates increased further with the spread of hypodermic administration of morphine. Courtwright DT, et al. [26] An examination of Courtwright's collected epidemiology data during these sixty years, more specifically from the Jacksonville Registration/Maintenance data for the years 1912 and 1913 revealed increase in the number of white females addicted to morphine, laudanum, heroin, gum opium, and cocaine collectively by 37.8 percent. The largest contribution to this increase was from morphine and cocaine addiction [26].

Data from the Addiction Severity Index Multimedia Version Connect database reported that women were 1.6 times more likely than men to report prescription opioid use [27]. Back SE, et al. compared opioid dependence profiles between men and women from national multisite effectiveness trials [28]. This investigation found that a significantly intense craving for opioids at treatment entry and significantly higher rates of comorbid psychiatric conditions and psychological symptoms among women were the motives for misuse prescription opioids among women. Back SE, et al. [28] These findings echo past data of similar profile traits of women addicted to heroin and opium in the 19th century reported by Courtwright [26]. Women who are victims of violence or of child-bearing age or belong to the LGBTQ community are at especially increased risk of the negative effects of opioid misuse and abuse. Koons AL, et al. [29] Both Kendall and Courtwright relate the described psychological and social profiles of drug addicts of the 19th century as white, upper-middle-class women whose addiction tended to be family-centered. They were fictionalized in literature, e. g., Mrs. Henry Lafayette Dubose, a character in Harper Lee's "To Kill a Mockingbird" [23-26].

Sex and Gender Differences in Opioid Analgesia

The conceptual differences between sex and gender can be identified using both physical science as well as behavioral science. Sex is a biological concept based on characteristics such as the difference in genitalia in male and female; while gender deals with personal, societal and cultural perceptions of sexuality, i.e., masculinity and femininity. Sex and gender differences have been demonstrated with how women respond and eliminate medications to include opioid analgesics. As previously mentioned, sex hormones can influence the perception of pain; but also, sex hormones can make women more sensitive than men to the effects of some drugs including opioids. The goal of clinical opioid analgesic pharmacology is to understand how to optimize the use of opioid anal-

gesics to minimize therapeutic opioid adverse event and enhance opioid therapeutic effectiveness. Regrettably, significant gaps still remain in the inclusion of women in clinical trials. Marrocco A, et al. [30] Specific drug pharmacokinetics and pharmacodynamics may differ between men and women. Soldin and Mattison [31] report that reviews of the Food and Drug Administration's Adverse Events Reporting System (AERS) suggest that women experience more drug-related adverse events and often these adverse events are described as more serious. Soldin OP, et al. [31] Physiological differences between males and females have been observed in plasma volume, body mass index, plasma proteins, body fat, cardiac output, liver blood flow, and hepatic enzyme activity; thus, influencing the hepatic clearance of drugs. Soldin OP, et al. [31] Further, there are known sex differences with all three major renal functions: glomerular filtration, tubular secretion, and tubular reabsorption.

Soldin OP, et al. [31] Morphine, which is a phenanthrene, acts as a pure agonist whose principal therapeutic action is analgesia. It binds and thus activates mu-1 and mu-2 opioid receptors at sites in the periaqueductal and periventricular gray matter, ventromedulla and spinal cord to produce analgesia.[9] Morphine has long been considered the gold standard of opioid agents. Smith RG, et al. [9] Morphine has been shown to be more potent and also exhibits a slower onset and offset in women. Soldin OP, et al. Sarton E, et al. [32,33] It has been established that women perceive more pain and require greater dosages of morphine to achieve the same antinociceptive effect as in men. Pieretti S, et al. Craft R. M, et al. [13,14,32] Soldin et al., offer an explanation for this as higher mu-receptor binding in various cortical and subcortical brain regions exhibited in women than in men. Soldin OP, et al. [32] Fillingim et al., highlight the data collected in a 2009 comprehensive review on sex-specific influences on pain, which reveal that women appear to be more sensitive to pain and also are more vulnerable to chronic, widespread, and post procedural pain conditions [34]. Finally, Averitt et al., present evidence that demonstrates a neural basis implicating sex differences in opioid metabolism and neuroimmune signaling with a focus on the periaqueductal gray as a sexual dimorphic core of descending opioid-induced inhibition [35]. They summarize the data to state that both preclinical and clinical research indicate that opioids are less effective in females to explain why women are more likely to be prescribed opioids at higher doses and for longer periods of time than men [35].

Opioid Litigation

Haffajee and Mello lead a discussion of the legal accountability of companies for supplying opioids to the prescription market [36]. Further, they describe the history of liability lawsuit against these companies, which commenced in the early 2000s but have increased in frequency and profile only in the recent years. One of the earliest of these suits was against Purdue Pharma. It was based on personal injury claims brought on behalf of addicts who had been overdosed. Haffajee, et al. [36] More claims alleged that opioid manufacturers deliberately withheld information about their products' dangers, misrepresenting them as safer than alternatives. Haffajee, et al. Ausness RC, et al. [36,37] A class action suit brought by a large group of similarly-situated individuals is one procedural strategy in substance-related litigation (such as those involving opioids and tobacco) that may be helpful in overcoming defenses based on users' conduct. Haffajee, et al. [36] The class action suit that shows the causal relationship between the companies' business practices and the harm is assessed at the group level with focus on statistical associations between product use and injury. Nevertheless, early attempts to bring class action suits against opioid manufacturers encountered procedural barriers. Because of the varying factual circumstances surrounding individuals' opioid use and clinical conditions, judges often deemed proposed class members to lack sufficiently common claims. Haffajee, et al. [36] It is hoped that litigation could also help alleviate the opioid epidemic by changing industry practices and building public awareness. Further, lawsuits may bring to light harmful, unethical, and even illegal business practices that sour the public opinion of opioid companies.

Haffajee, et al. [36] It is this author's stance that women are an "at risk population" due to sex and gender differentiated reaction to opioid pharmacology, opioid adverse effects, and opioid misuse when opioids are prescribed to them. The data on these female specific characteristics was available but not utilized by the stakeholders, namely, the opioid manufacturers, opioid prescribers, and opioid dispensers. Epidemiology centered on pain prevalence and the rate of opioid use among females allows for an inference that women often use substances differently than men and women can respond to substances differently. Moreover, women who use opioids may experience more physical effects and changes in their heart, blood vessels, and brain. Secondly, female-specific historical data centered on opioid use and misuse that renders females an "at-risk population" may have been overlooked by opioid manufacturers while detailing their product to providers. Finally, both gender and sex differences in opioid-mediated analgesia and opioid fate in humans have been studied for over past decades and this data was overlooked during the manufacture, delivery, prescribing and dispensing opioid analgesics, resulting in the first wave of the opioid crisis. It is this author's belief that more data may assist in getting legal remedies against those who may have caused the opioid crisis and establish for the future a logical approach to prescribing of opioids by acknowledging the non-symmetric axiom: females are not equal to males in terms of the opioid crisis.

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