JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń

Cite as: DOMIŃCZAK, Dominika, KUREK, Aleksandra, GŁOWACKA, Aleksandra, KAMINSKAYA, Anhelina, FERETYCKI, Hubert, SALAMA, Aladdin, SAVCHAK, Tetiana, GÓRECKI, Patryk, IVANCHUK, Sofiia and ABDULLA, Shafea. From Microglia to Stereotypes: The Impact of Sex and Gender on Pain Perception and Analgesic Response. Journal of Education, Health and Sport. 2026;93:72629. https://doi.org/10.12775/JEHS.2026.93.72629

ARTICLE TIMELINE
Received: 26.05.2026 Revised: 20.06.2026
Accepted: 20.06.2026 Published: 23.06.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

From Microglia to Stereotypes: The Impact of Sex and Gender on Pain Perception and Analgesic Response

Authors

Dominika Domińczak* (Corresponding Author), ORCID https://orcid.org/0009-0008-4911-622X
dominika.dominczak@stud.umed.lodz.pl
Medical University of Lodz, 4 Kościuszki Street, 90-419, Lodz, Poland

Aleksandra Kurek, ORCID https://orcid.org/0009-0008-9666-6638
aleksandrakurek01@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland.

Aleksandra Głowacka, ORCID https://orcid.org/0009-0009-2141-4978
a.glowacka@interia.pl
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland

Anhelina Kaminskaya, ORCID https://orcid.org/0009-0002-1900-1778
kam.angelina1977@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland.

Hubert Feretycki, ORCID https://orcid.org/0009-0000-6497-4451
h.feretycki@gmail.com
Cardinal Stefan Wyszynski University in Warsaw, 5 Dewajtis Street, 01-815 Warsaw, Poland

Aladdin Salama, ORCID https://orcid.org/0009-0005-2941-1916
aladdin1710@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland.

Tetiana Savchak, ORCID https://orcid.org/0009-0002-6829-1281
taniasavchak02@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland.

Patryk Górecki, ORCID https://orcid.org/0009-0008-0437-6984
gpatryk631@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland

Sofiia Ivanchuk, ORCID https://orcid.org/0009-0007-0008-053X
sonyaivanchuk@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland

Shafea Abdulla, ORCID https://orcid.org/0009-0000-1256-8443
shafea2001@gmail.com
Medical University of Warsaw (WUM), 61 Żwirki i Wigury Street, 02-091 Warsaw, Poland

Abstract

Background: Despite the shift towards personalized medicine, pain management frequently relies on universal dosing based on a standard male model. Both biological sex and socio-cultural gender significantly influence nociception and treatment efficacy, contributing to the clinical "pain gap" and unequal care.

Aim: To systematize current knowledge regarding sex-specific differences in pain neurobiology, perception and the pharmacokinetics of commonly used analgesics.

Materials and methods: A narrative literature review was concluded, analyzing recent experimental and clinical studies focusing on pain neuroimmunology, pharmacokinetics and clinical outcomes in both sexes.

Results: Evidence demonstrates marked sexual dimorphism in pain processing. Chronic pain is mediated by microglia in males and T-cells in females. Pharmacokinetically, females exhibit a higher volume of distribution for lipophilic drugs and higher CYP3A4 activity, but slower phase II metabolism and lower glomerular filtration rates. Clinically, this translates to distinct efficacy profiles and higher risks of adverse drug reactions for NSAIDs and mu-opioids in women, whereas kappa-opioids agonists provide superior analgesia in females.

Conclusions: Universal analgesic dosing is inadequate, often exposing women to suboptimal pain relief and increased toxicity. Integrating sex as a biological variable and implementing SAGER guidelines in future research are essential for equitable, precision pain medicine.

Key words: sex characteristics, gender bias, pain perception, pharmacokinetics, analgesics, precision medicine

1. Introduction

Modern medicine is experiencing a dynamic transformation, shifting from a "one-size-fits-all" approach toward personalized medicine. In this new paradigm, sex emerges as one of the most critical determinants of health, influencing not only the predisposition to specific diseases but also their pathophysiology, clinical presentation, and response to pharmacotherapy [1]. Nevertheless, the full integration of the concept of sex- and gender-specific medicine into standard clinical practice remains a significant challenge.

Historically, clinical and pharmacological research for decades relied on a standard reference model: a healthy, adult male weighing approximately 70 kg [2]. Women, particularly those of childbearing potential, were systematically excluded from the early phases of clinical trials, a practice that was effectively formalized by FDA guidelines in 1977 [3]. This approach, driven by the desire to protect against the potential teratogenic effects of novel compounds and the aim to eliminate variables arising from hormonal fluctuations, led to a massive knowledge gap. It resulted in the direct extrapolation of outcomes obtained in male populations to female

populations, which to this day remains the primary cause of suboptimal drug dosing and a nearly twofold higher risk of adverse drug reactions in women [2].

One of the fields where the consequences of this phenomenon are most evident is pain management. Although pain is a universal experience, scientific evidence unequivocally indicates that its perception, modulation, and nociceptive mechanisms exhibit significant sexual dimorphism [4]. This biological divergence is further exacerbated by the so-called "pain gap"—socio-cultural determinants and gender stereotypes that cause women's pain symptoms to be more frequently downplayed by healthcare professionals and misattributed to psychogenic factors [5]. Furthermore, the efficacy, safety profile, and pharmacokinetics of commonly used analgesics demonstrate substantial variations depending on the patient's sex [6].

The primary aim of this review is to systematize current knowledge regarding sex-specific differences in pain perception and the efficacy of analgesic pharmacotherapy. This paper discusses neurobiological variations, the impact of hormonal fluctuations, and pharmacokinetic differences that dictate the clinical response to the most used classes of analgesics.

2. Conceptual distinction: biological sex versus socio-cultural gender in the clinical context

In scientific literature and routine clinical practice, the terms "sex" and "gender" are frequently, yet erroneously, used interchangeably. Understanding the distinction between these constructs is crucial for the proper interpretation of pain mechanisms, the evaluation of research outcomes, and the personalization and optimization of therapy [7].

Biological sex is an objective, genetically determined trait (defined by the presence of XX or XY chromosomes) that dictates an organism's anatomy, physiology, and sex steroid profile [7]. Sex-based differences directly translate to distinct neurobiology of nociceptive processes, varying density and sensitivity of opioid receptors in the central nervous system (CNS), and disparities in the pharmacokinetics of analgesics [8].

Conversely, socio-cultural gender is a complex, multidimensional construct encompassing the social roles, behaviors, expressions, and identities that a given society attributes to women and men [7]. In the clinical context, gender plays a decisive role in how patients communicate their symptoms and when they choose to seek medical attention. Deep-rooted cultural norms

subject men to societal pressure that dictates stoicism and the concealment of pain, whereas women are expected to express pain more freely—a behavior that is often erroneously interpreted as hypersensitivity [9].

These disparities in socialization and ingrained stereotypes contribute to a phenomenon widely described in the literature as the "pain gap." Studies demonstrate that, owing to the implicit bias of healthcare professionals, physiological pain symptoms reported by women are significantly more often dismissed or downplayed. This issue manifests across multiple levels of healthcare but is particularly pronounced in the diagnosis of chronic pain and the management of acute pain [10].

In the context of chronic pain, the pain gap presents a systematic, years-long delay in the diagnostic process. A glaring example of this phenomenon is endometriosis, a systemic disease characterized by an exceptionally severe pain component. Epidemiological data indicate that an average of 7 to 10 years elapses between the onset of initial symptoms and the establishment of a definitive diagnosis. Such a drastic delay stems largely from the "normalization of female pain"—the erroneous social and medical assumption that severe menstrual or pelvic pain constitutes a physiological norm. This misconception discourages physicians from promptly initiating comprehensive diagnostic workups and specialized treatments [11].

Conversely, regarding acute pain, these disparities become evident in the speed and intensity of pharmacological interventions. Retrospective analyses from emergency departments (EDs) consistently demonstrate that women presenting with acute abdominal or chest pain wait significantly longer—often by several dozen minutes—to receive their first dose of analgesia compared to men presenting with analogous symptoms [12]. This discrepancy arises from the fact that pain in men is almost immediately categorized as an objective somatic symptom, whereas women's complaints are more frequently attributed to psychogenic factors [10].

This leads to a dangerous therapeutic paradox and biases in medical documentation. In clinical notes, pain in female patients is sometimes described using subjective terms such as "emotional," "exaggerated," or "hysterical." Consequently, female patients are not only less likely to receive adequate doses of potent analgesics (e.g., opioids) necessary for acute pain management, but they are also disproportionately more likely to be prescribed sedatives—such as benzodiazepines—and antidepressants as a substitute for appropriate analgesic therapy [12,13].

3. Neurobiological and immunological foundations of differences in pain perception

Sex differences in pain perception are the result of complex interactions at the level of the peripheral and central nervous systems, the immune system, and the endocrine system.

3.1. The peripheral nervous system and the endogenous opioid system

Differences in nociception begin at the level of peripheral tissues. Morphological studies of the skin reveal sex differences in the density of nociceptive innervation. For instance, it has been demonstrated that females are characterized by a significantly higher density of thin nerve fibers in the epidermis (e.g., in the facial region) compared to males [14]. Furthermore, biochemical analyses indicate the presence of sexual dimorphism within the endogenous opioid system. Positron emission tomography (PET) studies have visualized that, in response to a painful stimulus, healthy men exhibit a substantially greater release of endogenous endorphins and activation of **μ**-opioid receptors in brain structures, translating to more effective endogenous pain inhibition than in women [15].

3.2. Functional pain processing in the brain (fMRI)

Functional magnetic resonance imaging (fMRI) studies provide further evidence that male and female brains process nociceptive information differently. In men, exposure to acute pain more strongly activates cognitive and analytical regions (such as the prefrontal cortex), which is associated with heightened threat assessment and escape planning. Conversely, in women, painful stimuli induce greater activation in limbic system areas, including the amygdala and the anterior cingulate cortex. This indicates a stronger affective-emotional component in pain processing among female patients, which may partially explain the higher comorbidity of chronic pain with mood and anxiety disorders in women [16].

3.3. The role of microglia and T cells – a neuroimmunological breakthrough

The most groundbreaking discoveries of recent years concern the close crosstalk between the central nervous and immune systems in the generation of chronic and neuropathic pain. Historically, it was assumed that the mechanisms underlying neuropathic pain were universal across both sexes. Animal model studies, published in *Nature Neuroscience* in 2015, overturned this dogma by revealing a drastic cellular dimorphism [17].

It was proven that in males, the activation of microglia—immune cells residing in the spinal cord—plays a pivotal role in the development of pain hypersensitivity (allodynia). Here, the transmission of pain signals depends on the P2X4 receptor and brain-derived neurotrophic factor (BDNF). Surprisingly, inhibiting microglial activity in females produces no analgesic effect. In females, the adaptive immune system, specifically T cells infiltrating the meninges and spinal cord, is responsible for maintaining the chronic pain state [17,18].

Fascinatingly, newer analyses demonstrate the exceptional plasticity of this system, which is highly dependent on the hormonal milieu. Ovariectomy or the exogenous administration of testosterone in females causes them to "switch" to the male-typical, microglia-dependent pathophysiological pain pathway. This discovery carries monumental pharmacological implications, as it suggests that novel drugs targeting microglial inhibition (glial inhibitors), currently under intensive development by pharmaceutical companies, may only prove effective in male patients or in females with artificially elevated androgen levels [18,19].

3.4. The modulatory influence of sex steroids

The clinical presentation of pain is continuously modified by gonadal hormones. Testosterone exhibits a proven antinociceptive effect. Higher androgen levels elevate the pain threshold and partially protect against the development of various pain syndromes, corroborated by the fact that men suffering from hypogonadism report musculoskeletal pain symptoms significantly more often [20].

The role of female hormones, particularly estrogens, is characterized by a complex, biphasic mechanism of action dependent on the dynamics of their concentration changes. Stable, high concentrations of estrogens (e.g., during late pregnancy) exert a robust analgesic effect by promoting the activation of descending antinociceptive pathways. Conversely, sudden fluctuations and drops in estrogen levels—observed during the luteal phase of the menstrual cycle or the perimenopausal period—exert a strong pronociceptive effect. They cause a reduction in the pain threshold and sensitize the central nervous system, which in clinical practice manifests as the well-known phenomenon of exacerbation of migraines, fibromyalgia symptoms, or joint pain during specific days of the cycle [21].

4. Pharmacokinetic differences determining treatment response

Although biological sex significantly determines pharmacokinetic processes (ADME: absorption, distribution, metabolism, and excretion), the dosing standards for most analgesics

still rely on universal weight-based calculations. This phenomenon leads to a situation where women are statistically more prone to adverse drug reactions and, in some instances, suboptimal therapeutic efficacy [22].

4.1. Gastrointestinal absorption

The absorption process of orally administered drugs exhibits significant dimorphism. Physiologically, women are characterized by a higher (less acidic) gastric pH, as well as slower gastric emptying and intestinal transit times, which is largely modulated by the inhibitory effect of progesterone on smooth muscle [22]. In the case of oral analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs), slower transit may result in a delayed time to reach maximum blood concentration (Cmax). In acute pain management, female patients may perceive this as a weaker or delayed onset of drug action [23].

4.2. Distribution: Body composition and plasma protein binding

Differences in the volume of distribution arise from dimorphism in body composition and varying profiles of plasma proteins. On average, women are characterized by a 10–15% higher body fat content and a lower total body water (TBW) volume [24]. Consequently, highly lipophilic drugs, such as fentanyl or buprenorphine, reach a significantly larger volume of distribution in female patients, accumulating in adipose tissue. This phenomenon leads to a prolonged half-life and significantly increases the risk of delayed respiratory depression. Furthermore, drug distribution is strictly dependent on plasma protein binding. Analgesics circulate in the blood in a protein-bound state (representing the inactive fraction) and in a free state, which is responsible for the therapeutic effect. While the concentration of albumin, which binds acidic drugs (e.g., ibuprofen), is similar in both sexes, the concentration of alpha-1-acid glycoprotein (AAG), which binds basic drugs (including opioids and local anesthetics), is significantly lower in women. This effect is further potentiated by the influence of estrogens [25]. As a result, female patients may reach a higher, potentially toxic free fraction of these substances in the blood.

4.3. Hepatic metabolism: CYP450 isoenzymes and phase II reactions

The most substantial sex differences concern hepatic metabolism, which encompasses phase I (oxidation, reduction) and phase II (conjugation) reactions. In the first phase, the cytochrome P450 (CYP) family of isoenzymes plays a crucial role. The activity of the CYP3A4

isoenzyme, responsible for the metabolism of approximately 50% of all clinically used drugs, including many opioids, is 20–30% higher in women [26]. Higher activity in females is also observed for the CYP2D6 isoenzyme, which is responsible for converting prodrugs, such as tramadol or codeine, into their active forms (O-desmethyltramadol and morphine, respectively). A faster conversion via this pathway may result in a sudden, dangerous spike in the blood concentration of the active substance in female patients [27]. An inverse trend applies to phase II reactions. Processes such as glucuronidation generally proceed significantly faster in men. Because this pathway represents the primary route of elimination for morphine and paracetamol, slower phase II metabolism in women explains why standard doses of these drugs circulate in their bodies for a longer duration. This provides more potent analgesia but simultaneously generates a higher risk of adverse drug reactions, including postoperative nausea and vomiting (PONV) [27,28].

4.4. Renal elimination and membrane transporters

Renal excretion of drugs is a function of the glomerular filtration rate (GFR) and active tubular secretion. The average GFR in women is approximately 10–20% lower than in men, directly resulting from lower muscle mass [29]. This is of critical importance for the elimination of active metabolites, such as morphine-6-glucuronide (M6G), which subsequently accumulate much faster in female patients. Furthermore, recent studies indicate a distinct dimorphism in the expression of renal organic cation transporters and P-glycoprotein, which actively extrude drugs from cells. Although their precise clinical significance in pain pharmacotherapy requires further investigation, they constitute another crucial element influencing the variability in drug elimination [30].

4.5. Intra-individual variability: Menstrual cycle and exogenous hormones

Unlike in men, the pharmacokinetic profile of women of reproductive age is not static; it undergoes dynamic changes in rhythm with the menstrual cycle and under the influence of oral hormonal therapy (OHT). During the luteal phase of the cycle, when progesterone concentrations peak, there is a maximum slowing of gastrointestinal peristalsis, which can noticeably modify the absorption profile of orally administered drugs [23]. An additional factor influencing pharmacokinetics involves exogenous estrogens and progestins, which act as potent modulators of hepatic enzymes. The use of oral contraceptives induces glucuronidation processes and increases the clearance of paracetamol, which in clinical

practice may necessitate shortening the dosing intervals. Concurrently, these hormones function as inhibitors for multiple CYP isoenzymes, which in turn elevates the risk of toxicity from co-analgesics, such as antidepressants routinely used in the treatment of neuropathic pain [31,25].

5. Efficacy and safety profile of selected analgesic classes

The neurobiological, endocrinological, and pharmacokinetic differences described in previous chapters find their direct reflection in daily clinical practice. The response to standard pain management exhibits clear sexual dimorphism, which applies to both the magnitude of the analgesic effect and the frequency of adverse reactions. Understanding these differences is essential for the rational, evidence-based medicine (EBM) selection of an active substance tailored to the patient's sex.

5.1. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol

Nonsteroidal anti-inflammatory drugs are among the most frequently used analgesics and co-analgesics worldwide; however, their efficacy is not identical in both sexes. Experimental models and clinical observations unequivocally indicate that men achieve a higher and more predictable degree of pain relief following the administration of classical NSAIDs, such as ibuprofen [32]. Conversely, from the perspective of the safety profile, women bear a higher risk of toxicity. Due to the differences in gastrointestinal physiology, women are statistically more susceptible to gastrointestinal complications (e.g., upper gastrointestinal bleeding) during chronic NSAID therapy [33]. In the case of paracetamol (acetaminophen), although the higher activity of conjugating enzymes (phase II) in men leads to its faster clearance, a higher risk of acute hepatotoxicity following a drug overdose is observed in women. This is most likely associated with a lower baseline liver mass in women and smaller systemic reserves of glutathione, which is necessary for the neutralization of the toxic paracetamol metabolite, NAPQI [33].

5.2. Opioids and the diverse role of receptor subtypes

Differences in the response to potent opioid drugs represent one of the most well-documented and fascinating areas of sex-specific pharmacology. This dimorphism stems from the varying density, distribution, and reactivity of individual opioid receptor subtypes in the central nervous system. Classical opioid drugs, such as morphine and fentanyl, exhibit strong agonist

affinity for μ (mu) receptors. Meta-analyses of clinical trials demonstrate that women typically achieve stronger, deeper, and more prolonged analgesia following morphine administration than men [34]. However, this higher efficacy is inextricably linked to a dramatically higher incidence of adverse reactions. Women experience postoperative nausea and vomiting (PONV) and deeper sedation significantly more often, which very frequently necessitates premature dose reduction or even the discontinuation of opioid therapy [34].

A true breakthrough in understanding the mechanisms of pain relief, however, was brought about by research on κ (kappa) receptors. A research team led by Gear demonstrated that drugs acting as agonists or partial agonist-antagonists of κ receptors—such as nalbuphine, butorphanol, or pentazocine—exhibit remarkably stronger analgesic effects in women, whereas in men, their analgesic efficacy is low or even negligible [35]. This discovery unequivocally confirms that nociceptive pathways in females rely to a much greater extent on kappa receptor-dependent signaling. This knowledge is of fundamental importance in anesthesiology and acute pain management, providing physicians with the opportunity to select a drug with a mechanism precisely tailored to the female patient's neurobiology.

5.3. Co-analgesics in the treatment of chronic and neuropathic pain

The management of chronic and neuropathic pain syndromes almost invariably requires the use of so-called co-analgesics, which primarily include tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and gabapentinoids (gabapentin, pregabalin). As demonstrated in the translational models discussed in chapter three, chronic neuropathic pain in males depends on microglial activation, whereas in females, it relies on T-cell infiltration. This distinct cellular etiology may partially explain the clinically observed differences in the response to neuromodulatory drugs, which often exhibit limited efficacy in female patients [18,36]. Furthermore, pharmacokinetic data indicate that women are more likely to discontinue pain-directed antidepressant therapy due to severe, intolerable adverse effects, such as weight gain, significant daytime sedation, or cardiac arrhythmias (QT interval prolongation). This stems directly from the differences in the distribution of these lipophilic molecules within adipose tissue and the fact that their hepatic metabolism is inhibited by female hormones [36]. A comprehensive summary of the sex-based differences in pharmacokinetics and clinical responses to the discussed analgesics is presented in Table 1.

Table 1. Summary of key sex-based differences in the pharmacokinetics, pharmacodynamics, and clinical outcomes of major analgesic classes.

Drug Class / Specific Drug	Primary Pharmacological Mechanism	Key Sex-Based Differences (PK/PD)	Clinical Implications & Recommendations
μ-Opioid Agonists *(e.g., Morphine, Fentanyl)*	**μ**-opioid receptor activation; Hepatic Phase II metabolism (Morphine) or CYP3A4 (Fentanyl).	Females exhibit slower glucuronidation (Phase II), leading to prolonged circulation of morphine and its active metabolites. Higher CYP3A4 activity alters the clearance of lipophilic opioids like fentanyl.	Women generally achieve stronger and longer-lasting analgesia but experience a significantly higher incidence of postoperative nausea and vomiting (PONV) and sedation. Consider dose reduction in female patients.
κ-Opioid Agonists *(e.g., Nalbuphine, Butorphanol, Pentazocine)*	**κ** -opioid receptor agonism / partial antagonism.	Female nociceptive pathways and the endogenous opioid system rely more heavily on κ-receptor signaling compared to males.	These agents provide highly effective analgesia in women, whereas they exhibit limited or negligible analgesic effects in men. They should be

			considered a preferred option for acute pain management in female patients.
NSAIDs & Paracetamol *(e.g., Ibuprofen, Acetaminophen)*	Cyclooxygenase (COX) inhibition (NSAIDs); complex central mechanisms (Paracetamol).	Slower gastrointestinal transit in females delays NSAID C(max). Men have faster Phase II clearance of paracetamol, but women have lower baseline hepatic glutathione reserves.	Men show more predictable and potent pain relief with classical NSAIDs. Women are at higher risk for NSAID-induced gastrointestinal bleeding and face a greater risk of acute hepatotoxicity following a paracetamol overdose.
Co-analgesics for Neuropathic Pain *(e.g., TCAs, SNRIs)*	Neuromodulation via neurotransmitter (serotonin/norepinephrine) reuptake inhibition.	Higher body fat percentage in females increases the volume of distribution (Vd) for these lipophilic drugs. Estrogens act as inhibitors for the hepatic metabolism of several antidepressants.	Women experience more severe and intolerable side effects (e.g., weight gain, excessive sedation, QT interval prolongation), leading to higher treatment discontinuation rates. Dose titration should be gradual and closely monitored.

Source: Author's own elaboration.

6. Summary and Conclusions

The presented literature review unequivocally demonstrates that sexual dimorphism in the context of pain management is a multidimensional phenomenon, extending far beyond simple anatomical differences. Biological sex determines the functioning of the nociceptive system at the cellular and immunological levels and dictates distinct pharmacokinetic processes, such as drug distribution and the activity of cytochrome P450 isoenzymes. In turn, socio-cultural gender and its associated stereotypes still alarmingly impact the doctor-patient relationship, contributing to the phenomenon of the "pain gap" and the suboptimal treatment of women [10,37].

In the era of evidence-based medicine (EBM) and the pursuit of fully personalized therapy, ignoring the patient's sex as a crucial biological variable is a fundamental clinical oversight. To improve the safety and efficacy of pharmacotherapy, it is imperative to move away from universal drug dosing based on the standard 70-kilogram male model. Implementing this knowledge into clinical practice requires physicians to more vigilantly monitor female patients for adverse drug reactions (e.g., gastrointestinal events following NSAID administration or central nervous system effects after opioids) and to be more open to modifying doses and dosing intervals, particularly in the context of the menstrual cycle or the use of hormonal contraception [22,34].

However, for a systemic change in clinical guidelines to be possible, a revolution at the design stage of scientific research is necessary. It is absolutely essential to promote the application of the international SAGER (Sex and Gender Equity in Research) guidelines. These guidelines obligate researchers not only to equally include both sexes in clinical trials, but above all, to rigorously report and stratify results by sex [38]. Only in this way will modern medicine be able to offer male and female patients' treatment that is precise, safe, and free from bias.

Disclosure

Supplementary Materials

Not applicable.

Author Contributions

Conceptualization: Dominika Domińczak, Aleksandra Kurek, Aleksandra Głowacka

Methodology: Dominika Domińczak, Aleksandra Kurek, Aleksandra Głowacka

Formal analysis: Patryk Górecki, Sofiia Ivanchuk, Anhelina Kaminskaya

Investigation: Hubert Feretycki, Tetiana Savchak
Resources: Aleksandra Głowacka, Hubert Feretycki
Data curation: Tetiana Savchak, Aladdin Salama
Writing – original draft preparation: Dominika Domińczak, Aleksandra Kurek, Aleksandra Głowacka
Writing – review and editing: Aladdin Salama, Shafea Abdulla, Sofiia Ivanchuk
Visualization: Anhelina Kaminskaya, Patryk Górecki
Supervision: Dominika Domińczak, Aleksandra Kurek, Shafea Abdulla

All authors have read and agreed to the published version of the manuscript.

Funding
No external funding was received to perform this review.

Institutional Review Board Statement
Not applicable.

Informed Consent Statement
Not applicable.

Data Availability Statement
Data sharing is not applicable to this article because no new data was created or analyzed in this study.

Acknowledgements
Not applicable.

Conflicts of Interest
The authors declare no conflict of interest regarding the publication of this paper.

AI Declaration
Declaration of the use of generative AI and AI-assisted technologies in the writing process. In preparing this work, the authors used ChatGPT for the purpose of assisting with grammar and

readability. After using this tool, the authors reviewed and edited the content as needed and accepted full responsibility for the substantive content of the publication.

References

1. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020;396(10250):565-582. https://doi.org/10.1016/S0140-6736(20)31561-0
2. Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. Biol Sex Differ. 2020;11(1):32. https://doi.org/10.1186/s13293-020-00308-5
3. Liu KA, Mager NA. Women's involvement in clinical trials: historical perspective and future implications. Pharm Pract (Granada). 2016;14(1):708. https://doi.org/10.18549/PharmPract.2016.01.708
4. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth. 2013;111(1):52-58. https://doi.org/10.1093/bja/aet127
5. Hoffmann DE, Tarzian AJ. The girl who cried pain: a bias against women in the treatment of pain. J Law Med Ethics. 2001;29(1):13-27. https://doi.org/10.1111/j.1748-720x.2001.tb00037.x
6. Grabek, A., Babiak, R., Bajak et al. (2023). Pain - ways to determine the intensity and the choice of the appropriate form of treatment. *Journal of Education, Health and Sport*, *39*(1), 55–69. https://doi.org/10.12775/JEHS.2023.39.01.005
7. Tannenbaum C, Ellis RP, Eyssel F, Zou J, Schiebinger L. Sex and gender analysis improves science and engineering. Nature. 2019;575(7781):137-146. https://doi.org/10.1038/s41586-019-1657-6
8. Mogil JS. Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon. Nat Rev Neurosci. 2012;13(12):859-866. https://doi.org/10.1038/nrn3360
9. Samulowitz A, Gremyr I, Eriksson E, Hensing G. "Brave Men" and "Emotional Women": A Theory-Guided Literature Review on Gender Bias in Health Care and

Gendered Norms towards Patients with Chronic Pain. Pain Res Manag. 2018;2018:6358624. https://doi.org/10.1155/2018/6358624

10. Zhang L, Losin EAR, Ashar YK, Koban L, Wager TD. Gender Biases in Estimation of Others' Pain. J Pain. 2021;22(9):1048-1059. https://doi.org/10.1016/j.jpain.2021.03.001
11. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. Am J Obstet Gynecol. 2019;220(4):354.e1-354.e12. https://doi.org/10.1016/j.ajog.2018.12.039
12. Chen EH, Shofer FS, Dean AJ, et al. Gender disparity in analgesic treatment of emergency department patients with acute abdominal pain. Acad Emerg Med. 2008;15(5):414-418. https://doi.org/10.1111/j.1553-2712.2008.00100.x
13. Richardson J, Holdcroft A. Gender differences and pain medication. Womens Health (Lond). 2009;5(1):79-90. https://doi.org/10.2217/17455057.5.1.79
14. Frot M, Feine JS, Bushnell CM. Sex differences in pain perception and anxiety. A psychophysical study with topical capsaicin. Pain. 2004;108(3):230-236. https://doi.org/10.1016/j.pain.2003.11.017
15. Zubieta JK, Smith YR, Bueller JA, et al. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science. 2001;293(5528):311-315. https://doi.org/10.1126/science.1060952
16. Gupta A, Mayer EA, Fling C, et al. Sex-based differences in brain alterations across chronic pain conditions. J Neurosci Res. 2017;95(1-2):604-616. https://doi.org/10.1002/jnr.23856
17. Sorge RE, Mapplebeck JC, Rosen S, et al. Different immune cells mediate mechanical pain hypersensitivity in male and female mice. Nat Neurosci. 2015;18(8):1081-1083. https://doi.org/10.1038/nn.4053
18. Mogil JS. Qualitative sex differences in pain processing: emerging evidence of a biased literature. Nat Rev Neurosci. 2020;21(7):353-365. https://doi.org/10.1038/s41583-020-0310-6
19. Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. J Neurosci Res. 2017;95(1-2):500-508. https://doi.org/10.1002/jnr.23831
20. Maurer AJ, Lissounov A, Knezevic I, Candido KD, Knezevic NN. Pain and sex hormones: a review of current understanding. Pain Manag. 2016;6(3):285-296. https://doi.org/10.2217/pmt-2015-0002
21. Craft RM. Modulation of pain by estrogens. Pain. 2007;132 Suppl 1:S3-S12. https://doi.org/10.1016/j.pain.2007.09.028

22. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48(3):143-157. https://doi.org/10.2165/00003088-200948030-00001
23. Freire AC, Basit AW, Choudhary R, Piong CW, Merchant HA. Does sex matter? The influence of gender on gastrointestinal physiology and drug delivery. Int J Pharm. 2011;415(1-2):15-28. https://doi.org/10.1016/j.ijpharm.2011.04.069
24. Anderson GD. Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. J Womens Health (Larchmt). 2005;14(1):19-29. https://doi.org/10.1089/jwh.2005.14.19
25. Gandhi M, Aweeka F, Greenblatt RM, Blaschke TF. Sex differences in pharmacokinetics and pharmacodynamics. Annu Rev Pharmacol Toxicol. 2004;44:499-523. https://doi.org/10.1146/annurev.pharmtox.44.101802.121453
26. Schwartz JB. The current state of knowledge on age, sex, and their interactions on clinical pharmacology. Clin Pharmacol Ther. 2007;82(1):87-96. https://doi.org/10.1038/sj.clpt.6100226
27. Islam MM, Iqbal U, Walther BA, et al. Gender-based personalized pharmacotherapy: a systematic review. Arch Gynecol Obstet. 2017;295(6):1305-1317. https://doi.org/10.1007/s00404-017-4363-3
28. Fillingim RB, Ness TJ, Glover TL, et al. Morphine responses and experimental pain: sex differences in side effects and cardiovascular responses but not analgesia. J Pain. 2005;6(2):116-124.
29. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-Related Differences in Pharmacokinetics and Pharmacodynamics of Frequently Prescribed Drugs: A Review of the Literature. Adv Ther. 2020;37(2):644-655. https://doi.org/10.1007/s12325-019-01201-3
30. Chu X, Bleasby K, Evers R. Species differences in drug transporters and implications for translating preclinical findings to humans. Expert Opin Drug Metab Toxicol. 2013;9(3):237-252. https://doi.org/10.1517/17425255.2013.741589
31. Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet. 1990;18(6):472-484. https://doi.org/10.2165/00003088-199018060-00004
32. Walker JS, Carmody JJ. Experimental pain in healthy human subjects: gender differences in nociception and in response to ibuprofen. Anesth Analg. 1998;86(6):1257-1262. https://doi.org/10.1097/00000539-199806000-00023

33. Franconi F, Campesi I. Pharmacogenomics, pharmacokinetics and pharmacodynamics: interaction with biological differences between men and women. Br J Pharmacol. 2014;171(3):580-594. https://doi.org/10.1111/bph.12362
34. Niesters M, Dahan A, Kest B, et al. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain. 2010;151(1):61-68. https://doi.org/10.1016/j.pain.2010.06.012
35. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. Nat Med. 1996;2(11):1248-1250. https://doi.org/10.1038/nm1196-1248
36. Shansky RM, Murphy AZ. Considering sex as a biological variable will require a global shift in science culture. Nat Neurosci. 2021;24(4):457-464. https://doi.org/10.1038/s41593-021-00806-8
37. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. Nature. 2014;509(7500):282-283. https://doi.org/10.1038/509282a
38. Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. Res Integr Peer Rev. 2016;1:2. https://doi.org/10.1186/s41073-016-0007-6