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CONTENTS

Editorial

Filippou Dimitrios *Ethical Frontiers in Modern Medicine: Humanity at the Crossroads of Innovation*

Brief Communication

Papadopoulos Vasileios, *The Making of Man and the Epistemology of Uncertainty: Gregory of Nyssa and the Biomedical Quest for Knowledge*

Historical Vignette

Perdikakis Miltiadis, Papadimitrakis Dimosthenis, Sinou Nikoleta, Sinou Natalia, Filippou Dimitrios *From Oath to Algorithm: The Evolution of Medical Ethics from Hippocrates to the Digital Age*

Case Report

Domouliaka Evdoxia, Vasilipoulou Anastasia, Dafni Maria, Apostolopoulos Alexandros, Lioni Athina, Tzavara Vasiliki *A Case of Fat Embolism Syndrome after Elective Hip Arthroplasty*

Review

Aikaterini Kontekaki, Sinou Nikoleta, Chrysiikos Dimosthenis, Troupis Theodoros, Filippou Dimitrios *The Neuroendocrine Model of Premenstrual Dysphoric Disorder (PMDD)- Functional Impairment as the stable underestimated axis: A Narrative and Mechanistic Review*

Editorial

Ethical Frontiers in Modern Medicine: Humanity at the Crossroads of Innovation

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In the swiftly evolving realm of healthcare, our shared quest for innovation has opened remarkable avenues: genetic modification, artificial intelligence in diagnostics, precision healthcare, and regenerative treatments. However, alongside these advancements lies a concurrent narrative — one that tests our ethical principles and compels us to reconsider what it means to be a caregiver in the modern age. Medicine has continuously balanced science and humanity. The role of the physician has always extended beyond mere treatment; it has included compassion. Yet today, we find ourselves in an era where the distinction between what we are capable of and what is ethically justifiable becomes less defined. The ethical challenges we face are more than academic discussions; they influence patient interactions, resource distribution, and ultimately, the core of medical professionalism.

The Promise and Peril of Technological Medicine. The impact of technology on clinical practice has been transformative. AI now aids in interpreting radiology, predictive modeling, and patient assessment. Genomic sequencing enables us to anticipate disease predisposition long before they surface. Robotic-assisted surgery reduces invasiveness, while digital health solutions provide care outside conventional settings. Nevertheless, each breakthrough presents ethical ramifications. When algorithms determine care priorities, who is accountable for mistakes? Are we assured that AI, trained on biased data, does not reinforce healthcare inequalities? Furthermore, how can we maintain the essential human relationship between physician and patient when much of our interaction occurs through technology? There's growing apprehension that as medicine becomes driven by data, it risks losing its personal touch. Patients can be seen as data points, diminished to

risk assessments rather than valued individuals with unique concerns and lives. While efficiency is necessary, it must never compromise empathy. We must ensure that technological advancements act as enablers of healing — not replacements for human connection.

The Ethical Implications of Genomic Power. Few advancements stir as much excitement and apprehension as genetic medicine. The ability to alter the human genome brings remarkable prospects: eradicating inherited diseases, personalizing treatments, and perhaps even increasing longevity. Yet, history shows that unchecked power can lead to ethical dilemmas. CRISPR and related gene-editing methods pose serious moral questions. Should we modify the germline to avert diseases in future generations? How do we differentiate legitimate medical interventions from enhancements? The alluring dream of genetic perfection may reawaken detrimental biases, where societal value becomes linked to biological enhancement. Additionally, increased access to genetic testing introduces fresh anxieties. Patients now face knowledge about health predispositions that might never come to fruition. This “genetic awareness” can impose psychological burdens, strain familial relationships, and create challenges for insurers, employers, and policymakers. Hence, clinicians must extend their responsibilities beyond conveying results; they must support patients in navigating the emotional and existential impacts of their knowledge.

Inequality in an Era of Abundance. A striking paradox in modern medicine is that its achievements are not equally accessible. While certain regions advance toward personalized genomic treatments and robotic precision, others grapple with shortages in basic healthcare, clean

water, and maternal care. This widening divide between healthcare luxury and necessity emerges as one of the most significant ethical challenges today. Equity is not simply an issue of policy; it is an ethical responsibility. The legitimacy of any healthcare system hinges on its treatment of the most vulnerable individuals. As resources dwindle, clinicians face increasingly tough decisions over who receives cutting-edge interventions, who must wait, and who ends up overlooked. These choices, once limited to times of war and crisis, are now commonplace in healthcare settings worldwide. We cannot overlook that medical ethics function within systems influenced by socio-economic and political factors and deep-seated inequities. It is insufficient to discuss principles such as autonomy, beneficence, and justice in isolation. We must contemplate how these principles manifest when dealing with patients lacking insurance, those who are undocumented, or those who feel overlooked. Thus, the physician's obligation extends beyond clinical care — it demands advocacy for justice in healthcare policies.

End-of-Life Ethics and the Right to Die with Dignity. Even with our technological advancements, the specter of mortality remains a salient part of healthcare. The ability to prolong life has advanced faster than our ability to assess its quality. Intensive care units often sustain patients long after consciousness and connection have dissipated, forcing families to agonize over decisions between continuing treatment and compassionate cessation. The ethics surrounding end-of-life care encompass not only medical principles but also deeply human concerns. They compel us to explore what constitutes a dignified death — a notion that varies across cultures and beliefs. As physicians, we must approach this sensitive landscape with humility, accepting that our duty is not solely to prolong life but to alleviate suffering while respecting the dignity of each individual. Palliative care, once misconceived as a failure of medical intervention, should be seen as one of the most profound expressions of our profession. To provide comfort when a cure is no longer feasible represents one of medicine's highest callings. As we enhance tools for

prolonging life, we must also develop the wisdom to recognize when it is appropriate to let go.

The Doctor-Patient Relationship in a Fragmented World. Trust is a critical foundation of medical ethics. Yet today, trust, which used to be inherent, feels increasingly fragile. The commercialization of healthcare, pharmaceutical marketing, and bureaucratic pressures have diluted the integrity of the doctor-patient relationship. Today's healthcare professionals are often evaluated not based on their empathy but by productivity measures: patient volume, efficiency in documentation, and discharge rates. This trend toward industrialization compromises the relational core of medicine. When physicians must focus on paperwork over personal connections, they risk losing their role as compassionate caregivers. To restore humanity to healthcare, we need a conscious reorientation of values. We must prioritize meaningful dialogue with patients, actively listening to their concerns. Medical education should not only address clinical skills but also emphasize the importance of empathy, compassion, and the ability to share in patients' struggles. No algorithm can replicate the healing power found in genuine human interaction.

Artificial Intelligence and the Ethics of Delegation. Artificial intelligence stands as both a new frontier and a complex ethical challenge in healthcare. Predictive analytics can forecast critical events like cardiac arrest or sepsis with astonishing accuracy. Chatbots fill roles in mental health support, while algorithms assist in diagnostics and clinical judgments. However, AI lacks the capacity for moral reasoning. Machines cannot understand the nuances of a patient's experiences or the moral complexities that accompany uncertainty. Shifting clinical decision-making to algorithms raises accountability challenges: When AI recommendations lead to harm, who is at fault — the physician, the programmer, or the organization? Moreover, many AI systems operate as "black boxes," obscuring their decision-making processes. Clinicians may have to trust technology's outputs without fully comprehending the reasoning behind them, contradicting the transparency essential to ethical practice. To

responsibly incorporate AI, we must uphold the principle that technology should enhance, not replace, human judgment. Ethics oversight, regulatory bodies, and professional standards must evolve to keep pace with technological advances. The physician's role will increasingly transition from being the lone decision-maker to serving as a moral steward, ensuring that the systems they utilize amplify their capabilities without compromising their ethical foundation.

Reaffirming the Moral Identity of Medicine. In the midst of these transformations, the core of medicine must remain anchored in its moral identity: a commitment to relieve suffering and enhance human well-being. Ethics is not an add-on to medical practice; it's its cornerstone. As educators, we hold a crucial responsibility to nurture this moral awareness in the next generation of healthcare professionals. Medical education should weave ethics into the fabric of all training, from anatomy and physiology to clinical practice. Students must learn not only to diagnose but also to recognize moral dilemmas, reflect on their biases, and approach uncertainty with humility. Indeed, practicing medicine is as much a moral endeavor as it is a scientific one. Each decision we make — every prescription, every

interaction at the bedside — carries significant ethical weight.

A Call for Compassionate Modernity. The ethical challenges facing contemporary medicine are substantial, yet they are not impossible to navigate. The same creativity that drives scientific progress can also enhance ethical understanding. To advance, we must strive for what could be termed compassionate modernity — a progress that honors both the intellect and the spirit of medicine. This involves creating technologies that prioritize patients instead of systems. It entails supporting policies that emphasize fairness rather than profit. It underscores the notion that compassion, rather than mere efficiency, determines the quality of care. Additionally, it calls for recognizing that behind every statistic is a human narrative — a narrative that requires our focus, our dignity, and our understanding.

As we approach an era of remarkable medical advancements, the critical inquiry is not just about what medicine is capable of accomplishing, but rather what form of medicine we aspire to establish. Future evaluations will be based not on our inventions, but on our shared humanity.

Brief Communication

The Making of Man and the Epistemology of Uncertainty: Gregory of Nyssa and the Biomedical Quest for Knowledge

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Abstract

This article explores the epistemological parallels between the theological anthropology of Gregory of Nyssa and Bayesian models of learning, with a particular focus on their implications for biomedical reasoning and medical education. Drawing from Gregory's treatise "On the Making of Man", the human being is viewed as an evolving entity, advancing through freedom and experience toward truth. Similarly, Bayesian epistemology, widely applied in modern clinical reasoning and diagnostics, frames human understanding as a process of belief revision in light of evidence. By placing these two frameworks in dialogue, this essay proposes a model of knowledge that honors uncertainty, humility, and the iterative nature of discovery—values that are central to both theological insight and biomedical inquiry.

1. Prologue – An Unexpected Affinity

What connection could there be between a 4th-century Church Father and 21st-century biomedical science? At first glance, none [1]. Yet, delving into the writings of Gregory of Nyssa (Figure 1), particularly on how humans come to know, reveals profound resonances with modern epistemological frameworks used in medicine and health sciences. Gregory presents the human person as a being in motion—free, incomplete, progressing toward truth [2]. This resonates with statistical models, particularly Bayesian inference, that underpin much of contemporary clinical decision-making [3].



Figure 1. Saint Gregory of Nyssa

2. The Frequentist and the Bayesian approach in Statistics.

In the realm of statistical inference, two dominant paradigms shape how knowledge is derived from data: the frequentist and Bayesian approaches. Understanding their foundations is essential for appreciating how they intersect not only in scientific reasoning but also in theological reflection.

The frequentist approach defines probability as the long-run relative frequency of an event occurring across numerous trials. It presumes no prior belief—only observed outcomes matter. For example, in clinical trials, if a treatment yields recovery in 70 out of 100 patients, the success rate is considered to be 70%. This method emphasizes objectivity, replicability, and hypothesis testing through tools such as p-values and confidence intervals. It is deeply embedded in biomedical research methodology, where randomized controlled trials serve as the gold standard for establishing causality and therapeutic efficacy [4].

The Bayesian approach, by contrast, frames probability as a degree of belief or certainty about an event, which is updated as new evidence becomes available. This perspective begins with a 'prior'—an initial estimate based on background knowledge or subjective belief. As data accumulate, the prior is revised using Bayes' theorem to form a 'posterior' belief. In

medicine, this is reflected in diagnostic reasoning: a physician might initially suspect a condition based on symptoms (prior), but adjust their confidence based on test results (evidence). Bayesian methods are particularly useful in complex, individualized, or data-scarce contexts where rigid trial designs fall short (Figure 2).

The point of convergence between these approaches emerges in the theoretical limit of infinite data. As the sample size grows indefinitely, the subjective influence of the prior in Bayesian inference diminishes (Figure 3). Likewise, frequentist estimates become increasingly precise. In this asymptotic condition, both methods yield the same result: the true underlying probability. Philosophically, this moment resonates with Gregory of Nyssa's vision of eternal progress culminating in divine presence. Time, as the measure of gradual learning, dissolves. In statistics, infinite data removes uncertainty; in theology, infinite presence eliminates the need for faith. Both paths suggest that truth, ultimately, is not deduced but revealed.

3. The Human Person in Gregory of Nyssa: Image, Freedom, and Ascent. In "On the Making of Man", Gregory of Nyssa portrays humanity not as a finished product but as a dynamic entity, evolving toward perfection: 'The beginning of being is not the perfection of nature, but nature reaches perfection through progress' [5]. This theological anthropology emphasizes continual learning and moral freedom, concepts with striking implications for modern education in the health sciences, where the human being is not merely an object of study, but an evolving subject capable of reflection, adaptation, and growth.

4. Learning the World Without Presumptions: The Frequentist Approach. The frequentist approach to statistics defines probability as the long-run frequency of events. It begins without prior beliefs—only with empirical observations and repeated trials. In biomedical research, this manifests in randomized controlled trials, where inference is built on replication and statistical significance [6]. This methodological humility parallels Gregory's conception of the human condition: a being that

moves forward without full knowledge, shaped by what is observed and experienced.

5. Believing in Order to Learn: The Bayesian Perspective. In contrast, the Bayesian model acknowledges the presence of prior beliefs, updated as new data emerges. In clinical medicine, Bayesian reasoning has become integral to diagnostic algorithms and personalized treatment planning [7]. It echoes Gregory's view of human development: we are born with imprints of divine image—existential priors—that evolve through free decisions and spiritual encounters. Learning, in this light, is a recursive, adaptive process.

6. The Human as a Bayesian Being? A Theological Reflection. Can the human soul, in Gregory's vision, be seen as a Bayesian learner? Created in God's image, the human person begins life not from neutrality but from a meaningful origin. Life's experiences, like data, refine and reshape our moral and spiritual framework. Gregory writes: 'Even in the eternal journey of extension, there is no stagnation in the good' [8]. This mirrors the Bayesian model, where belief is never final, and understanding deepens with every encounter.

7. Bayesian Reasoning in Biomedical Contexts. Bayesian inference plays a crucial role in modern health sciences—from updating disease probabilities in differential diagnosis to machine learning in radiology [9]. Medical decision-making increasingly relies on models that revise their predictions based on accumulating evidence, reflecting a probabilistic understanding of human physiology and pathology. This approach requires physicians not only to understand data, but to inhabit a mindset of humility and adaptability—qualities Gregory deemed essential in the soul's ascent toward divine truth.

8. When Time Ceases: Infinity as a Point of Convergence. As more data accumulates, Bayesian and frequentist approaches tend to converge—uncertainty gives way to clarity. Similarly, Gregory teaches that while human life is characterized by gradual growth, ultimate knowledge transcends time and culminates in divine presence. 'Then the good is no longer seen

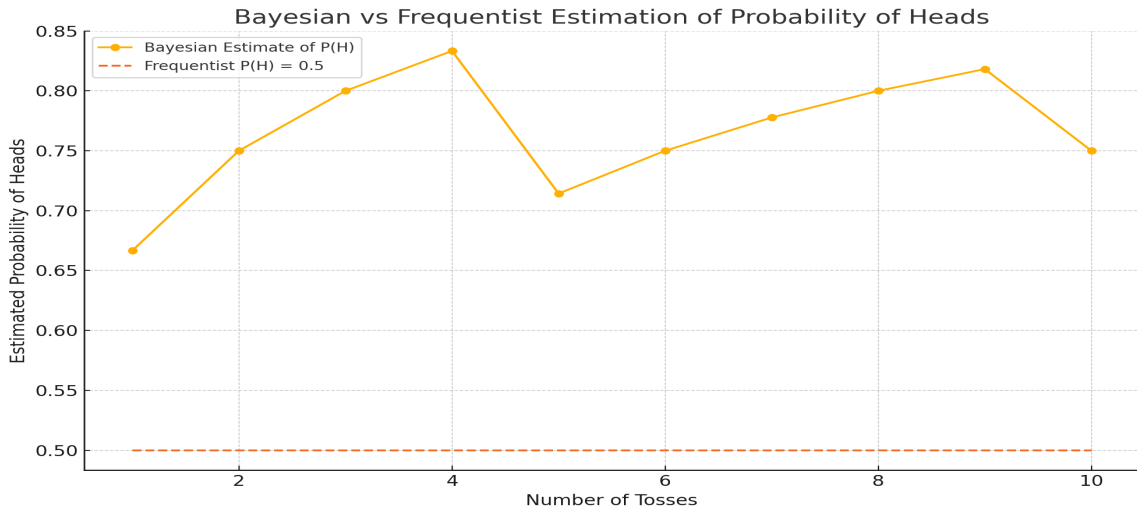


Figure 2. We flip a theoretically honest coin 10 times, and we observe 8 times heads (H) and 2 times tails (T) in a sequence “HHHHTHHHT”. The Bayesian estimate starts at 0.5 (with a uniform prior) and gradually shifts toward the observed data, increasing as more heads appear in the sequence. The frequentist model remains fixed, assuming a fair coin throughout.

through faith, but God is known through the presence of light' [8]. In both science and theology, there is a point beyond which analysis ceases—where truth is no longer inferred but encountered.

9. Conclusion – Journey, Not Destination.

This dialogue between Gregory of Nyssa and statistical epistemology reveals a shared vision:

that knowledge is never static, but a journey shaped by experience, belief, and revision. In biomedical education and practice, acknowledging this dynamic is essential. It cultivates practitioners who are intellectually humble, epistemologically vigilant, and ethically aware.

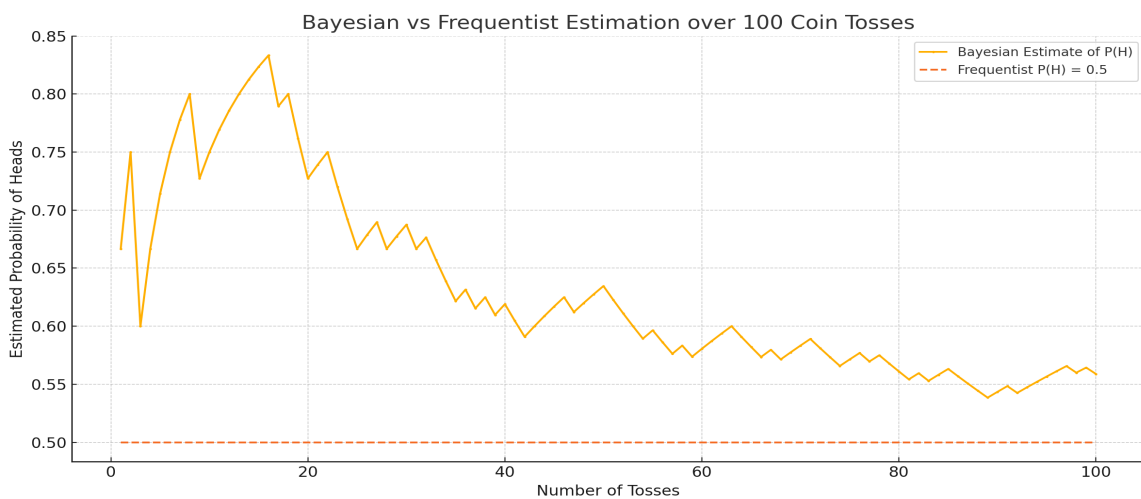


Figure 3. We asked ChatGPT to toss an honest coin 100 times; the result was “HHTTHHHHTHHHHHHHTTT HHTTTHTHTHTTTHTHTTTHHHHTHHHTTTTHTTTHHHHTTTHTHHHTTTHTHTTTHTHTTT TTTHTHHHHHTT” (56 H and 44 T). We observe that as the sample size grows, the subjective influence of the prior in Bayesian inference diminishes.

Theological anthropology and statistical reasoning converge in affirming that truth—whether clinical or spiritual—is best approached not with finality, but with reverent inquiry.

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Historical Vignette

From Oath to Algorithm: The Evolution of Medical Ethics from Hippocrates to the Digital Age

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Abstract

The Hippocratic Oath has long served as the moral cornerstone of Western medical practice, emphasizing beneficence, non-maleficence, confidentiality, and professional integrity. Yet the ethical landscape of contemporary medicine differs profoundly from that envisioned by Hippocrates more than two millennia ago. Modern clinicians face complex dilemmas arising from technological innovation, patient autonomy, global inequities, and artificial intelligence. This review explores the evolution of medical ethics from the classical principles articulated in the Hippocratic Oath to the multifaceted framework guiding today's medical professionals. It argues that while the form of ethical reasoning has changed, its underlying spirit — compassion and responsibility towards the patient — must remain constant.

Keywords: *Hippocratic oath, medical ethics, modern bioethics, critical comparison, history of medicine*

Introduction

The Hippocratic Oath, dating back to the fifth century BC, is often regarded as one of the earliest established codes of medical ethics. It arose from the rich cultural and philosophical heritage of ancient Greece and articulated the sacred bond between physicians, patients, and mentors, grounded in loyalty, humility, and a commitment to non-maleficence [1]. Over the years, this oath transitioned from a solemn promise of ethical duty to a ceremonial milestone for physicians across the globe.

Today's healthcare environment is markedly different from that of ancient Greece. Modern medical practitioners operate within systems shaped by technology, legal frameworks, patient autonomy, and social responsibility [2]. The ethical landscape of the twenty-first century encompasses not only clinical practice but also areas like genetics, patient data protection, end-of-life choices, and global disparities. This article delves into the core ethical values of the Hippocratic tradition and explores those shaping contemporary medicine, focusing on both their shared foundations and the emerging differences.

Materials and Methods

The bibliography for the current review article was accumulated from book chapters which discuss the Hippocratic Oath and articles from the PubMed online database. Furthermore, international conventions related to the research topic were also explored. Regarding the PubMed search, the research method followed the PRISMA 2020 statement guidelines. The terms used regarding this search were "medical ethics", "end of life situations", "euthanasia", "machine ethics". Following the identification and screening of the studies provided, 10 PubMed articles were decided suitable for the current review.

Discussion

The Hippocratic Ethical Foundation. The classic Hippocratic Oath enshrines several vital tenets: (a) Beneficence and non-maleficence, «I will apply dietary measures for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice." (b) Confidentiality, "What I may see or hear in the course of treatment... I will keep to myself." (c) Professional solidarity and humility: physicians affirmed loyalty to their mentors and successors

and avoided claiming divine authority over life and death, and (d) Moral integrity and purity: The Oath prohibits practices such as abortion, euthanasia, and sexual misconduct, reflecting the moral and societal norms of the time [3] (Figure 1).

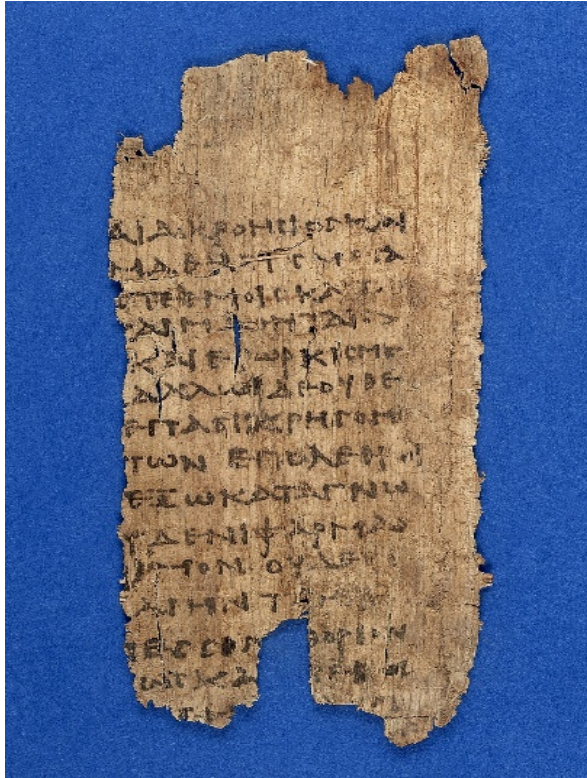


Figure 1: Fragment of the Hippocratic Oath

These values were essentially paternalistic. The physician, perceived as morally superior and intellectually capable, made decisions for the patient's welfare without their input. In intimate, close-knit communities where medical care was restricted to managing symptoms and prognosing conditions, this paternalism was functional and generally accepted [4].

It is also noteworthy that in ancient Athens the medical approach differed between the civilians and the slaves. As Plato explains in *Laws* (IV, 720), free civilians were provided with healthcare more adherent to autonomy than the non-civilians. They should be “persuaded” by the physician regarding their treatment and decide whether they wanted to be treated. However, even in that case, the physician was the one to decide and implement his therapy of choice [5].

The Rise of Modern Bioethics. The most significant shift in medical ethics since ancient times occurred in the twentieth century. Historical events like the heinous Nazi medical tests, the Tuskegee Syphilis Study, and the growing recognition of patient rights redefined the moral responsibilities of physicians [6,7]. These catalysts gave rise to modern bioethics, highlighting autonomy, justice, and respect for individuals as foundational ethical principles. The Belmont Report, published in 1979, crystallized these ideals into three core tenets: respect for humans, beneficence, and justice (Figure 2). This marked a pivotal transition from Hippocratic paternalism to a patient-centered ethical framework. Physicians transitioned from being moral gatekeepers acting on behalf of patients to collaborative partners working alongside them [8]. The Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, published in 1997, also known as Oviedo Convention, further discussed the patient's rights and is regarded as a cornerstone for European healthcare applications [9]. The rapid evolution of biomedical technology—from organ transplants to artificial insemination and genetic engineering—has also prompted ethical queries Hippocrates could not have fathomed. The focus has shifted from individual patient care to societal consequences, from moral intents to procedural ethics.

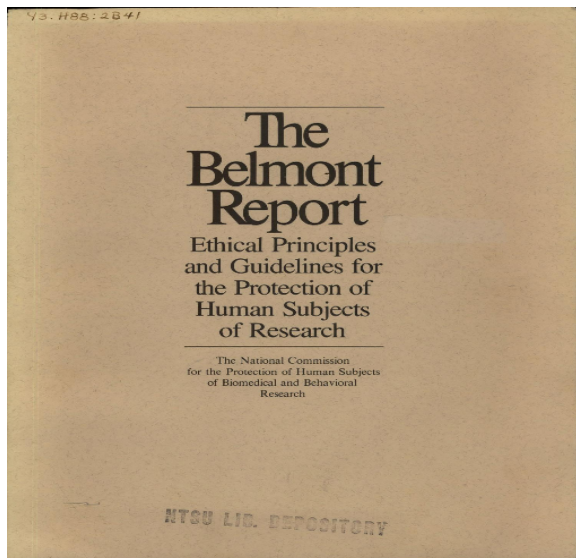


Figure 2: The Belmont Report

Autonomy and the Transformation of the Doctor-Patient Relationship. Perhaps the most notable transformation has been the elevation of patient autonomy. In the traditional model, medical judgment rested solely with the physician. Today, informed consent is a pivotal element of ethical medical practice. This change mirrors broader philosophical shifts in Western ideology, emphasizing individual rights and self-determination [10]. While Hippocrates saw the physician as a paternal guide, contemporary ethics recognizes the patient as a moral agent capable of making informed choices about their own health.

However, this shift has its moral complexities. Modern clinicians must balance respect for patient autonomy with their professional duties and expertise. When patients refuse life-saving treatments or demand untested options, physicians find themselves at odds between the Hippocratic imperative to "do good" and modern respect for personal choice [11,12].

The Expanding Scope of Medical Responsibility. Even though the Hippocratic physician focused on individual care, today's physician navigates a complicated web of social, economic, and environmental influences. Issues such as public health, global disparities, and environmental sustainability have emerged as crucial ethical concerns. Topics like vaccine access, antibiotic resistance, and climate change illustrate that physicians' responsibilities now extend beyond individual

patient care to the broader community [13]. The COVID-19 pandemic has thrust clinicians into complex decisions about resource allocation that blur the lines between personal and societal responsibilities [14]. These dilemmas necessitate an ethical framework rooted not only in compassion but also in justice—a concept largely absent from the Hippocratic Oath.

Technological Transformation and the Ethics of Knowledge. Innovations in genomics, artificial intelligence, and digital health have significantly reshaped medical ethics. The authority of physicians, historically founded on experiential knowledge, is increasingly shared with algorithms and databases. Genetic testing raises deep ethical questions surrounding privacy, discrimination, and psychological impacts [15]. Furthermore, artificial intelligence complicates traditional accountability: If an AI misdiagnoses a patient, who holds ethical and legal responsibility [16]?

These challenges embody a new ethical horizon that reinterprets the principle of non-maleficence. In today's context, "to do no harm" necessitates safeguarding data integrity, preventing bias in algorithms, and ensuring transparent decision-making. The traditional notion of "first, do no harm" has broadened beyond clinical action to encompass digital ethics.

End-of-Life Ethics and the Re-definition of "Harm". In the Hippocratic tradition, physicians swore to avoid administering deadly medications, even at a patient's request. This restriction was grounded in both moral and religious convictions regarding the sanctity of life. In contrast, contemporary ethics acknowledges the nuanced complexities of suffering and validates patient choice as life approaches its end. Current debates on euthanasia, assisted dying, and the withdrawal of life support reveal the tensions between classical prohibitions and modern compassion [17].

While Hippocrates opposed hastening death, today's practitioners might view prolonging futile suffering as a form of harm. The ethical inquiry is no longer solely about whether to

intervene but also about when to refrain [18]. Palliative care, which prioritizes dignity and alleviating suffering, exemplifies a synthesis of ancient compassion and modern ethical reflection.

The Commercialization of Medicine.

Hippocratic ethics emerged from a perspective where medicine was a calling rather than a business, with the physician's loyalty being personal, not corporate. In contrast, today's healthcare exists within a market-driven framework where profit, litigation, and administrative processes often guide care decisions. This commercialization introduces significant ethical challenges: conflicts of interest in research, aggressive pharmaceutical marketing, and unequal access to care. The critical question then becomes whether physicians can uphold the spirit of the Oath in a profit-driven environment. Some experts suggest that ethical medical practice today necessitates not just individual virtue but also institutional reform to align organizational priorities with patient well-being [19].

Additionally, the commercialization and expansion of medicine raises fundamental questions about the physician himself. According to the Hippocratic Corpus, a physician that is a lover of wisdom is "isotheos", equal to god. Wisdom and medicine are not distant from each other. It is, therefore, evident that a physician in antiquity was not a mere professional, he was a multifarious personality, a wise man, a mystic of the world's secrets. The modern physician is therefore called to decide upon the way he wants to perform medicine. Is it going to be a healing process for both the mind and the body, a mystagogy of purification of the patient, or a simple transaction without a deeper meaning which leaves both parties unaffected?

Continuity and Change. Despite dramatic contextual shifts, the moral essence of Hippocratic ethics endures. The Oath's emphasis on compassion, integrity, and confidentiality remains relevant. What has shifted is not the ethical purpose of medicine, but the intricacies of its moral context. While modern medicine has incorporated a broader

ethical vocabulary that includes autonomy, justice, and human rights, its core mission remains the same: alleviating suffering and fostering human flourishing [20]. The challenge for contemporary physicians lies in interpreting timeless virtues amid current realities, ensuring beneficence takes cultural diversity into account, safeguarding confidentiality in digital contexts, and rethinking non-maleficence in light of technological and systemic risks.

Conclusions

The evolution from the Hippocratic Oath to modern bioethics mirrors the progression of both medicine and humanity. What began as a personal moral covenant has transformed into a nuanced, interdisciplinary dialogue encompassing philosophy, law, technology, and social justice. Nonetheless, one fundamental truth endures: medicine must remain a moral pursuit. The Oath serves as a reminder that the essence of healing is rooted not in algorithms or regulations, but in empathy, humility, and an unwavering commitment to well-being. As we confront the ethical complexities of the digital age, we must honor the spirit, if not the exact words, of Hippocrates. Even as instruments evolve, our responsibility to the individual—fragile, hopeful, and worthy of dignity—remains timeless.

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Case Report

A Case of Fat Embolism Syndrome after Elective Hip Arthroplasty

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Abstract

Fat embolism syndrome (FES) is a rare clinical entity caused by the release of fat globules in blood circulation. It presents with pulmonary as well as systemic symptoms and is usually observed in connection to long bone fractures and orthopaedic procedures such as arthroplasties. In literature, case reports of FES are numbered, and diagnosis can be challenging as there is no pathognomonic sign or symptom for FES. The authors present the case of a 68-year-old male with dyspnea and altered mental status following elective arthroplasty. After extensive work-up and exclusion of other likely clinical entities, the authors reached the diagnosis of fat embolism syndrome. Supportive care was administered without anticoagulant agents or corticosteroids with subsequent recovery and discharge of the patient. The diagnosis of FES requires a high level of clinical suspicion and can often be elusive. The authors highlight the importance of timely diagnosis and supportive care.

Keywords: fat emboli syndrome, hip arthroplasty, elective arthroplasty, orthopaedics

Introduction

Fat embolism (FE) is the presence of fat globules in pulmonary circulation. Fat embolism syndrome (FES) is a rare clinical syndrome caused by fat released into blood circulation and includes pulmonary and systemic symptoms [1-3]. The majority of cases of FES are related to long bone fractures and orthopaedic procedures such as arthroplasties [1-3]. Incidence is variable with rates of FES ranging from 1% to 10% in trauma patients, 0.1% to 12% after total knee arthroplasty and 0.6% to 10% following total hip replacement [2-4]. Regarding the pathogenesis of FES, there are two main mechanisms described in literature: first, the mechanical theory where fat emboli enter the bloodstream through disrupted tissues and, second, the biochemical theory where intermediaries of fat are released and cause inflammation [3-5]. However, the exact pathophysiology of FES remains unknown. FES can present with a classic triad of non-specific symptoms including hypoxemia, neurologic abnormalities, and the presentation of a petechial rash. Chest radiographs are normal in

the majority of cases. CT scan may reveal well-demarcated ground glass opacities or ill-defined centrilobular nodules [3-5]. The diagnosis requires a high level of clinical suspicion as there is no pathognomonic sign or symptom of FES and in this case further imaging with CT scan is indicated. Treatment of FES is supportive with fluid resuscitation and oxygenation of the patient. The importance of early immobilization of long bone fractures and further staged definitive fixation in polytrauma patients has been well established [6]. The administration of prophylactic corticosteroids remains controversial and is not routinely used [4-6].

In this paper, we present the case of a 68-year-old male with a sudden onset of dyspnea and altered mental status occurring within hours from an elective right hip arthroplasty. After extensive diagnostic investigation and exclusion of other likely diagnoses, the clinical presentation was attributed to FES. Following supportive care and close monitoring, the patient displayed clinical and laboratory improvement leading to his discharge after 10 days of hospitalization. This case report

demonstrates the high degree of clinical suspicion required for timely diagnosis and the sufficiency of supportive treatment for the achievement of a favorable outcome.

Case Presentation

Medical history & clinical presentation

A 68-year-old male presented at the emergency department due to dyspnea and altered mental status with progressive deterioration over a span of 3 days. It was reported that the patient had undergone elective hip arthroplasty 3 days earlier in another hospital while the onset of symptoms was noted a few hours post-operatively. His medical history consisted of arterial hypertension and chronic kidney disease undergoing haemodialysis for the past 8 years.

At the emergency department, the patient was afebrile and haemodynamically stable, mildly tachycardic (approximately 105-110 bpm) and tachypnoeic (approximately 25 breaths/minute) while he presented with severe hypoxemia requiring oxygenation with a non-rebreather mask. Auscultation of the respiratory system revealed crackles in both lungs. From a neurological standpoint, the patient was confused, disoriented in time and place, his eyes were automatically open with pupils of the same size and reactive to light, he responded to verbal commands or questions with inappropriate words, he localized pain while he maintained movement in all four limbs without presenting any specific focal symptoms. The rest of the physical examination revealed rhythmic heart sounds without any additional murmurs, no jugular vein distention or palpable edema, mild sensitivity upon palpation of the abdomen as well as a haematoma around the surgical area/incision without concomitant signs of infection. Laboratory analysis showed a marked inflammatory syndrome with elevated CRP (347 mg/l, NR: < 3) and fibrinogen (1078 mg/dl, NR: 200 - 400), a mildly elevated total neutrophil count (76,4%) with a normal total WBC count (9.400/ μ l), while CPK and d-dimers values were also elevated (1768 u/l, NR: < 170

and 2.72 μ g/ml, NR: < 0.50 respectively).

Differential diagnosis & work up.

Taking under consideration the aforementioned clinical presentation and history, our differential diagnosis included the following: septic syndrome due to infection (pulmonary infection - possibly inspiration post extubation, CNS infection, vascular infection, surgical site infection), pulmonary embolism, pulmonary oedema, stroke (possibly ischaemic), fat embolism syndrome.

Examining the possibility of infection, blood cultures were obtained although no pathogen was isolated. Urinalysis did not reveal specific findings while urine culture was sterile. To rule out a CNS infection, a brain CT was performed and showed no abnormalities. Lumbar puncture revealed 1 lymphocyte and slightly elevated glucose in the CNS fluid, while PCR and culture tests were negative. Finally, the surgical site did not present any sign of infection throughout the duration of the hospitalization of the patient.

Due to the clinical presentation (severe hypoxaemia, tachycardia) and the relevant history of recent surgery, a lung CT was performed which excluded the possibility of pulmonary embolism but showed ground-glass lesions in both lungs. Furthermore, cardiology consultation was conducted with an echocardiogram which did not reveal any signs of volume overload or pulmonary hypertension. Moreover, a brain MRI was performed after admission which did not show any specific pathologic findings thus excluding the diagnosis of a cerebral event.

Treatment & outcome

After thorough diagnostic investigation which excluded all other possible differential diagnoses, the presenting signs and symptoms of the patient were attributed to fat embolism syndrome post-arthroplasty of the right hip. Although no petechiae or other type of rash was recorded, our patient met 2 out of 3 major criteria set by Gurd and Wilson thus making fat embolism syndrome a probable diagnosis in this

case. Indeed, the patient received supportive treatment (oxygenation through a non-rebreather mask) without any anticoagulant agents or corticosteroids. Throughout his hospitalization, he remained haemodynamically stable with no need for administration of intravenous fluids or vasopressors. Consequently, clinical improvement was noted with return of level of consciousness and communication to pre-surgery status and complete weaning of oxygen therapy. The patient was discharged after 10 days of hospitalization

Discussion

FES is considered to be a post-traumatic complication most commonly associated with long bone fractures or pelvic fractures. Fat embolism was first described by Zenker in 1861 [1, 7], who first diagnosed the presence of fat droplets in lung capillaries of a railroad worker that sustained crush injury and eventually passed away [7].

Aetiology of FES is mainly divided into traumatic and non-traumatic causes. Traumatic causes include orthopaedic conditions such as long bone or pelvic fractures, blunt force trauma, soft tissue injuries, burns, cardiopulmonary resuscitation compressions, etc. Although rare, non-traumatic conditions such as corticosteroid therapy, pancreatitis, haemoglobinopathies (sickle cell disease), liposuction, bone-marrow or lung transplantation and hip or knee arthroplasties are also associated with FES [1-4]. Although fat embolism is believed to occur to a greater or lesser extent in the majority of patients sustaining trauma, long bone or pelvic fractures and relevant arthroplasties, the clinical manifestation of fat embolism syndrome is variable [3, 4, 8, 9]. Existing bibliography consists mainly of case reports of FES whereas prospective or retrospective cohort studies are numbered. Indeed, there are several cases with FES presented in the literature with sustained long bone or pelvic fractures in major trauma centres, with bilateral fractures being associated with a higher incidence of FES

compared to unilateral long bone fractures [6, 7, 10]. According to published literature, 1%-5% of patients sustaining long bone fractures or undergoing orthopaedic procedures can present with FES [3, 7, 11, 12]. There are numbered case reports in the literature describing fat embolism after elective total hip or knee arthroplasty [8, 13-15].

Symptom manifestation is variable and can occur from the first hour's post-admission to as long as 2 weeks after initial trauma or surgery, although usually symptoms present within 24 to 72 hours after the causative incident [1, 3, 7]. In many cases, FES has an insidious onset with dyspnea, tachypnoea and hypoxemia which may progress to acute respiratory distress syndrome (ARDS). Fifty percent of patients with FES develop respiratory failure that requires mechanical ventilation [7]. Neurologic sequelae are usually subsequent to respiratory symptoms, may be present in 80% of patients and are non-specific [7]. They may include confusion or agitation as well as neurologic deficits, seizures or even coma. Finally, the petechial rash, which is considered pathognomonic for FES, is present in 20%-50% of cases and is typically located at the neck, thorax, axillae, subconjunctival space and oral mucous membranes [1, 3, 7]. Patients can also present with other non-specific signs and symptoms such as fever, tachycardia, jaundice, retinal changes, oliguria, or anuria. Death usually occurs due to respiratory failure or right heart failure [7].

Laboratory analysis may reveal anaemia, thrombocytopenia, elevated bilirubin, acute kidney injury as well as elevated inflammatory markers (CRP, ESR) [4, 7]. Radiographic imaging can be helpful, mainly in the sense of excluding alternative diagnoses. Chest radiography is usually normal [1]. In patients with respiratory compromise, it may reveal bilateral infiltrates (diffuse or patchy) mimicking ARDS, pulmonary oedema, or infection [4, 7]. CRX can be useful in monitoring progression of pulmonary infiltrates in patients with pulmonary FES manifestations [16]. Findings in computed tomography of the thorax most commonly consist of ground glass

infiltrates (either patchy, well-demarcated or diffused) which can be accompanied with interlobular septal thickening resulting in the so-called “crazy paving” pattern but, they can also include pulmonary consolidation and nodular opacities (usually centrilobular) [4, 7, 14, 16]. In patients with altered mental state, brain CT can reveal diffuse oedema with scattered haemorrhagic elements but in the majority of cases no abnormality is observed [4]. Further evaluation with MRI of the brain can be helpful for early diagnosis, especially when the “starfield pattern” is observed (multiple, small, nonconfluent, hyperintense lesions on T2 weighted images located around the ventricles, under the cortex or in the deep white matter) [4, 6, 7].

It is important to note that there is no gold standard diagnostic test for FES thus making its diagnosis one of exclusion [1]. As the diagnosis can often be elusive, a high degree of clinical suspicion is a necessary prerequisite parallel to the exclusion of more common entities such as septic syndrome or pulmonary embolism. In this context, diagnosis of FES is made using diagnostic tools such as certain sets of clinical and laboratory criteria, although none of them are clinically validated or universally accepted [1-4]. Most commonly, the Gurd and Wilson’s criteria are used [3, 9, 17].

Treatment is mainly supportive. Important aspects include oxygenation support (as far as mechanical ventilation, should that be deemed necessary) and haemodynamic stabilization through fluid resuscitation with or without the administration of blood products and vasopressors, as needed [4, 6]. Several protocols for targeted treatment (dextran, heparin, steroids) have been applied throughout the years but they have not demonstrated any benefit as far as outcome and morbidity is concerned [4, 6].

Depending on the severity of initial presentation, the outcome of patients with FES can vary from full recovery to death. Even though there is an important degree of variability in existing literature, FES is associated with high mortality with overall mortality rates

ranging from 5%-20% [7]. Older people seem to be more gravely affected with mortality rates as high as 17.6% in patients over 65 years old [18]. However, it is documented that rates of full recovery are high when patients receive appropriate supportive treatment [6]. This finding highlights the importance of clinical suspicion of FES, timely and appropriate differential work-up and administration of proper supportive care.

In recent years, there has been a significant decrease in the incidence of FES in trauma patients. The establishment of treatment protocols such as damage control orthopaedics and early total care led to early stabilization of fractures within the first few days post injury that reduced the incidence of FES in polytrauma patients [6, 7]. However, there are not many clinical cases described in the literature regarding the association between FES and arthroplasties. Interestingly, there are 5 clinical cases of patients developing symptoms of FES following elective arthroplasty described in the literature over a 20-year period [3, 19]. The definitive diagnosis was made using clinical criteria, head and chest CT and brain MRI [3, 19]. Modifications of surgical techniques such as cementless arthroplasties have not shown to have lower incidence of FES however, irrigation and aspiration of bone marrow contents could decrease the incidence of FES [3, 19].

There are two main theories described in the literature regarding the mechanism of FES. On one hand, the mechanical theory suggests that fat droplets from bone marrow or adipose tissue enter systemic circulation through torn venules after trauma or medullary preparation during surgery. In hip arthroplasty the insertion of the femoral stem causes mechanical compression of the medullary canal [5]. In addition, during knee arthroplasty, the use of long-stemmed components and intramedullary alignment guides also lead to an increase in intramedullary pressure [9, 14, 19, 20]. On the other hand, the biochemical theory proposes those toxic intermediaries of fat cause inflammation and release cytokines [7, 12].

Gurd and Wilson's criteria	
Major	Minor
<ul style="list-style-type: none"> ● Petechiae ● Hypoxemia ● Altered mental status 	<ul style="list-style-type: none"> ● Tachycardia >120 bpm ● Fever ● Retinal changes (fat or petechiae) ● Jaundice ● Anuria or oliguria ● Thrombocytopenia ● Anemia ● High erythrocyte sedimentation rate ● Fat macroglobulinemia
FES diagnosis	2 major or 1 major + 4 minor

Table 1. Gurd and Wilson's criteria for the diagnosis of Fat embolism syndrome [3]

Conclusion

We presented the case of a 68-year-old male with FES after elective total hip arthroplasty. Main symptoms comprised of mental status alteration and acute respiratory failure with symptom manifestation occurring a few hours post-operatively. Through clinical examination and laboratory and imaging analysis, alternate diagnoses were excluded. The patient received supportive therapy with oxygenation without any anticoagulant agents or corticosteroids. Clinical suspicion of FES in combination with timely and appropriate supportive treatment led to a full recovery and discharge of the patient after 10 days of hospitalization.

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Review

The Neuroendocrine Model of Premenstrual Dysphoric Disorder (PMDD)- Functional Impairment as the stable underestimated axis: A Narrative and Mechanistic Review

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Abstract

Introduction: Premenstrual Dysphoric Disorder (PMDD) is an abnormal condition that extends beyond the framework of typical premenstrual symptoms and frequently results in significant functional impairment.

Methods: A scoping review was conducted in November 2025 following PRISMA-ScR guidelines. Four structured searches were performed in PubMed using predefined combinations of keywords related to PMDD, functional impairment, neurobiology, endocrinology, and symptomatology. Inclusion criteria encompassed peer-reviewed journal articles and final-stage papers published between 2016–2025. Out of 198 initially identified records, 24 met eligibility criteria and were included in the final synthesis.

Results: PMDD consistently emerged as a disorder rooted in altered neural sensitivity to ovarian steroid fluctuations, rather than abnormal hormone levels. Evidence highlighted dysregulated GABAergic and serotonergic signaling, impaired stress-response mechanisms, increased inflammatory activity, and trait-like disruptions in cortico-striatal-thalamic connectivity. Genetic and epigenetic contributions—including variations in GABA-receptor subunit genes and ESC/E(Z) complex dysregulation. Symptomatically, PMDD was associated with marked affective lability, cognitive dysfunction, and decreased executive functioning, resulting to an overall functional impairment. Diagnostic protocols and therapeutic options (SSRIs, hormonal therapies, neurosteroid antagonists, and cognitive-behavioral interventions) were described across studies.

Aim: The aim of this review is to synthesize current evidence on the biochemical, genetic, neuroendocrine, immunological, and neuroanatomical factors contributing to PMDD, to clarify functional impairment as the main inevitable result of the disorder.

Keywords: Premenstrual Dysphoric Disorder; Neuroendocrinology; Serotonin; GABA Receptors; Functional Impairment.

Introduction

Premenstrual Syndrome (PMS and Premenstrual Dysphoric Disorder (PMDD) are both associated with psychosomatic symptoms. According to the American College of Obstetricians and Gynecologists (ACOG), the former is a complex of distressing physical, behavioral, and affective symptoms among women of reproductive age, which usually occur the week before menstrual shedding and then fade away a few days later, whereas the latter is a pathological condition—a mood disorder that worsens during the second half of the cycle and is considered a severe or even disabling extended form of PMS [1]. The frequent confusion of these two terms may potentially lead to an underestimation of the

severity of PMDD symptoms, which we propose often result in significant functional impairment. PMS appears in 3-8% of women in reproductive age, whereas PMDD affects 2% [2]. The inappropriate application of diagnostic criteria had previously led to an overestimation of the prevalence of PMDD [2]. The purpose of this study is to examine, through an extensive review of the literature, the various biochemical, genetic, and neural factors that contribute to the development of PMDD, while simultaneously defining it as a disorder distinct from simple premenstrual syndrome. Furthermore, we explored current therapeutic approaches and diagnostic protocols. A central component of our investigation is the analysis of PMDD

symptomatology, which we aim to demonstrate is not merely a set of periodic psychosomatic complaints but rather a constellation of constant neuroendocrine disturbances rooted in its pathophysiology, ultimately leading to functional impairment.

Materials and Methods

The study was conducted during the month of November 2025. A thorough investigation was carried out using the published literature found in the PubMed and database, employing the following keywords: premenstrual dysphoric disorder (AND) functional impairment (1st search), premenstrual dysphoric disorder (AND) symptoms young women (2nd search), premenstrual dysphoric disorder (AND) neurology (3rd search), premenstrual dysphoric disorder (AND) endocrinology (4th search). To guarantee precision and completeness, data was collected through a standardized extraction form tailored to these keywords. The research was conducted in accordance with the PRISMA-ScR guidelines (Preferred Reporting Items for Systematic Reviews

and Meta-Analyses Extension for Scoping Reviews), which provides a systematic framework for performing scoping reviews. The inclusion criteria were a) studies published in a journal, b) final-stage papers, c) research papers and only selected systematic reviews and meta-analyses, possessing particular interest and referring mainly to specific guidelines, and d) articles from 2016 until now. In accordance with the PRISMA guidelines, a total of 198 records were initially identified through the 4-stage search on PubMed: 1st search- 54 results, 2nd search- 99 results, 3rd search-19 results and 4th search- 26 results. After a thorough screening 155 studies were excluded due to irrelevance of the title and abstract to PMDD’s mechanisms or symptoms. A further examination of the 43 remaining studies led to exclusion of 19, due to exclusive focus on special groups. Finally, 24 reports were assessed for eligibility, resulting in the exclusion of 174 articles in total. Thus, this specific article is founded on data sourced from 24 credible references (Figure 1).

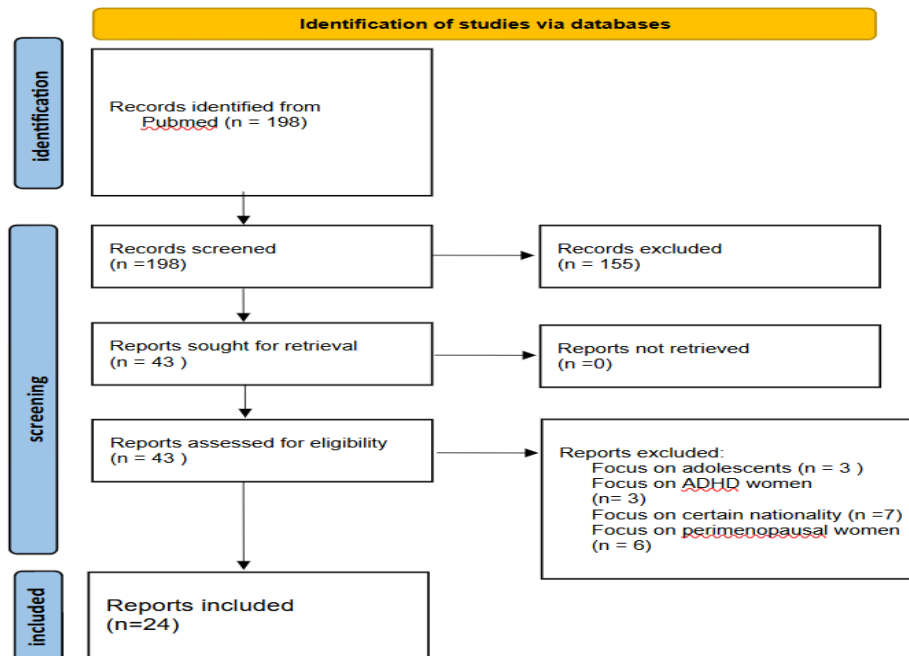


Figure 1. PRISMA Flowchart

Results

A thorough technique was used to evaluate the data according to the classification of the data mentioned above. While developing the themes, we took into consideration the mechanisms leading to PMDD and their effect on patient outcomes, as they are presented in all of the articles we selected as citations. In Table 1, we summarize the parts of the discussion included in the articles. Specifically, 20 articles referred to the vulnerability in steroids' fluctuation as a causal factor for PMDD, while 10 and 4 articles introduced serotonin response and inflammation as significant determinants of the disorder. Moreover, 8 reports showed specific genetic variations on receptor molecules which can lead to impaired response. Through further examination, 5 reports indicate that neuroanatomical variations explain if not cause the symptomatology of PMDD. Those symptoms were analyzed in all articles, while 15 give also an analytical presentation of the diagnostic protocols for the disorder. At the same time, 14 articles address the already used therapeutic methods or introduce new ideas. Lastly, 12 studies show the relevance of PMDD with other conditions that seem to appear to PMDD women. Functional impairment was indicated as the overall result of PMDD symptomatology in 20 studies, which revealed the effect of PMDD pathophysiology on a variety of normal mechanisms.

Discussion

Progesterone and Estradiol. It is essential to get cleared that PMDD is not a matter of the quantity of the steroid hormones -since the levels of progesterone during the luteal phase do not differ between healthy women and women with the condition- [3], but a well-established problem of the response to the changes of these hormones [4]. Fluctuations in estradiol and progesterone destabilize mood in susceptible women. Defining PMDD as a neuroendocrinological disorder [5]. Progesterone passes through the blood-brain barrier and

signals in the amygdala, hippocampus, hypothalamus, and frontal cortex [3], which are responsible for emotional and high-order cognitive responses. The problem seems to be attributed to the metabolite of progesterone, allopregnenolone, which acts as a strong positive modulator of the gamma-aminobutyric acid (GABA) receptor. Fluctuations on progesterone and thus allopregnenolone levels induce changes in the conformation of the GABA-A receptor sufficient to determine anxiety-like behaviors [3]. As far as estradiol is concerned, it is correlated with enhanced centrality of the right posterior cingulate gyrus (rPCG) and with higher scores on emotional and cognitive control, implying that estradiol-related modulation of network hubs may contribute to improved well-being and adaptive behavior. The sharp decline of estradiol during the luteal phase makes PMDD women even more vulnerable to psychological roller coasters [6].

Serotonin. Women with PMDD exhibit atypical serotonergic functioning, including reduced serotonin transporter density, lower peripheral serotonin concentrations during the luteal phase, and an enhanced serotonergic responsiveness in the follicular compared with the luteal phase. In addition, ovarian sex steroids modulate central serotonin availability by acting on monoamine oxidase (MAO), the enzyme responsible for serotonin degradation [3].

Inflammation. Emerging evidence suggests that immune-inflammatory mechanisms may play a contributory role in PMS/PMDD. Fluctuations of estradiol and progesterone in the late luteal phase appear to promote oxidative and inflammatory activity, including increased production of prostaglandins, cytokines, and matrix metalloproteinases. Although studies have reported elevated peripheral inflammatory markers—such as interleukins, TNF- α , CRP, and complement factors—the overall findings remain inconsistent, with some studies demonstrating reduced antioxidant capacity and others showing no significant alterations. Recent research highlights the potential involvement of

chemokines and a uterine brain signaling axis, as well as a central role for neuroinflammation

mediated through altered GABAergic function [7].

Study	Steroids	Serotonin	Inflammation	Genetics	Neuro-anatomy	Therapeutic means	Diagnosis protocols	Symptoms	Comorbid with other conditions	Functional impairment
Sayed 2025 [1]	YES	NO	NO	NO	NO	YES	YES	YES	YES	YES
Hausmann 2024 [2]	YES	YES	YES	YES	NO	YES	YES	YES	NO	YES
Tiranini 2022 [3]	YES	YES	NO	YES	NO	YES	NO	YES	NO	YES
Stierman 2023 [4]	YES	NO	NO	NO	NO	YES	NO	YES	NO	YES
Schiller 2016 [5]	YES	NO	NO	NO	NO	YES	NO	YES	YES	YES
Liparoti 2021 [6]	YES	YES	NO	NO	YES	NO	NO	YES	NO	YES
Beddig 2020 [7]	YES	NO	YES	YES	YES	YES	YES	YES	YES	NO
Hoffmann 2025 [8]	YES	NO	YES	NO	NO	NO	YES	YES	NO	YES
Islas 2023 [9]	YES	YES	YES	YES	NO	NO	YES	YES	YES	NO
Dubey 2017 [10]	YES	YES	NO	YES	NO	YES	YES	YES	YES	YES
Dubol 2022 [11]	YES	YES	NO	YES	YES	NO	NO	YES	NO	YES
Dan 2020 [12]	YES	YES	NO	NO	YES	NO	NO	YES	NO	YES
Jespersen 2024 [13]	YES	NO	NO	NO	NO	YES	NO	YES	NO	YES
Sikes 2023 [14]	YES	NO	NO	YES	NO	YES	NO	YES	NO	NO
Bixio 2017 [15]	YES	YES	NO	NO	NO	YES	NO	YES	NO	NO
Kaltsouni 2021 [16]	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES
Rabbani 2025 [17]	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES
Wu 2024 [18]	NO	NO	NO	NO	NO	NO	YES	YES	NO	YES
Mishra 2022 [19]	YES	NO	NO	NO	NO	YES	YES	YES	YES	YES
Naik 2023 [20]	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES
Prasad 2021 [21]	YES	YES	NO	NO	NO	YES	YES	YES	YES	YES
Lin 2024 [22]	YES	YES	NO	NO	NO	NO	YES	YES	YES	YES
Pekcetin 2021 [24]	NO	NO	NO	NO	NO	NO	YES	YES	YES	YES

Table 1. Topics addressed in articles

Stress. Patients with PMDD exhibit blunted cortisol peaks during the periovulatory phase, highlighting a potential interaction between stress-response mechanisms and serotonergic regulation, and furtherly explaining the intensity of depressive symptoms observed in the premenstrual phase [8]. Furthermore, it is indicated by a recent translational study, that chronic stress weakens the normal regulatory responses of the hypothalamic–pituitary–adrenal (HPA) axis to progesterone withdrawal, which

occurs in the late luteal period, resulting to abnormal responses [9].

Genetics. It is demonstrated that genes of the estrogen-sensitive ESC/E(Z) epigenetic complex are differentially expressed in women with PMDD, implicating dysregulated steroid-responsive gene silencing mechanisms [10]. The different response to estradiol leads to blunted endoplasmic reticulum stress response and altered intracellular calcium homeostasis, changes that may enhance neuronal excitability

and reduce sensitivity to GABA-A receptor modulators. Additionally, copy number variations in GABRB2, a GABA-A receptor subunit gene, demonstrate a direct genetic link between PMDD and altered GABAergic signaling. Collectively, these insights support a model in which genetic and epigenetic factors confer heightened behavioral sensitivity to ovarian steroids and may guide the development of targeted therapeutic approaches [3].

Neuronatomy. It is suggested that specific functional connections within cortico-striatal-thalamic circuits mediate the association between emotion regulation difficulties and PMDD. Reduced grey matter volume in ventral posterior cortical regions, the cerebellum, and specifically in the amygdala and putamen, aligns with the hypothesis of disrupted top-down emotional regulation. Grey matter morphology seems to function as neurobiological biomarker of PMDD, enforcing the view that PMDD is not limited to a biochemical disturbance but rather concerns the central processor of stimuli, namely the central nervous system (CNS) [11]. According to Rotem et al, there are trait-like alterations in the functional connectome of women with PMDD, characterized by cortical hypoconnectivity—particularly in the anterior temporal lobe—and subcortical hyperconnectivity involving the basal ganglia and thalamus, as well as reduced network segregation and increased integration. These network abnormalities were present across both the symptomatic luteal and asymptomatic follicular phases, suggesting a stable neural vulnerability rather than a state-dependent change [12].

Therapeutic means. Current evidence indicates that the management of PMS and PMDD varies substantially according to symptom severity and functional impairment [3]. Mild PMS without functional limitations may respond to lifestyle-based or complementary interventions, whereas PMDD requires pharmacological or psychotherapeutic treatment. Nutrient-related interventions, including zinc supplementation,

may exert beneficial anti-inflammatory, antioxidant, and neurotrophic effects, although evidence remains preliminary [3]. Among pharmacotherapies, selective serotonin reuptake inhibitors (SSRIs) demonstrate the strongest evidence base, with 60–70% of patients showing clinical improvement. Both continuous and luteal-phase dosing regimens are effective, though continuous administration may provide superior benefit in cases of severe symptomatology [13]. Combined estrogen–progesterone contraceptives [3], particularly monophasic formulations and those containing drospirenone, have also shown therapeutic potential, with one recent RCT indicating enhanced efficacy when combined with fluoxetine [3]. For refractory or severe presentations, GnRH agonists with add-back therapy may be considered [2]. The new therapeutic approach modulates the action of allopregnenolone on the GABA receptor of the brain neurotransmitters, given the plasticity of GABA-A receptor [14], using for example the GABAA modulating steroid antagonist (GAMSA) Sepranolone (UC1010) during the premenstrual phase [15]. As for the mediation of the aggressive response of the frontal cortex, selective progesterone receptor modulator (SPRM) is suggested [16]. Although the evidence for psychological interventions remains limited, preliminary data suggest that internet-based cognitive-behavioral therapy can meaningfully reduce PMS-related symptom burden [2].

Symptoms/ Diagnosis. It has been observed that cognitive shifts occur throughout the menstrual cycle; however, these changes are markedly more pronounced in women suffering from PMDD [17]. Specifically, women with PMDD show significant increases in negative affect and rumination and decreases in positive affect and self-acceptance toward the end of the cycle [7]. The difference between PMS and PMDD does not lie on the symptoms complex, but on its severity. Haussman et al suggests that PMS and PMDD are connected with a wide range of emotional, behavioral, and cognitive manifestations that

emerge during the luteal phase and tone down in the follicular phase [2]. Characteristic physical symptoms include mastodynia, headaches, abdominal bloating, fatigue-like complaints, and hot flashes. On average, symptoms persist for approximately six days per month, with peak severity occurring from four days before to three days after the onset of menstruation. The affective symptoms, which frequently predominate, include depressed mood, irritability, anxiety, feelings of tension, anger outbursts, increased appetite up to binge-eating episodes, rejection sensitivity, and loss of interest [2]. Age, age at menarche, income, menstrual cycle, menstrual symptoms, physical activity, and caffeine intake are indicated as independent influencing factors of PMDD in adult working women [18]. With regard to hereditary risk factors, genetic polymorphisms in the ESR1 gene, which encodes the estrogen receptor- α , are being discussed [2]. Prior traumatic events, a history of mental disorders, peripartum depression, obesity, smoking, alcohol use, and heavy drinking are also considered risk factors for PMDD [19].

The major symptoms of PMDD function as diagnostic markers in clinical practice. Currently, PMDD is listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) as a separate entity under Depressive disorders, with 4 diagnostic criteria. If at least 1 of these 4 criteria is met, the diagnosis leads to PMS [5]. The cut-off point between PMS and PMDD lies on the presence of more than 5 symptoms of the following [2]: depression, hopelessness, affective lability, anger and irritability, decreased interest in usual activities, short attention span, lethargy or lack of energy, change in appetite (overeating and cravings), insomnia or hypesomnia, subjective sense of being overwhelmed, other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, or weight gain [19]. These symptoms establish the 1st Criterion, while the rest define if the severity of the symptoms interferes with social, sexual, occupational

functioning, if they are discretely related to the menstrual cycle and if they are confirmed by prospective daily ratings [20].

A Meta-Analysis held in 2021 indicates that women with PMDD are almost seven times at higher risk of suicide attempt and almost four times as likely to exhibit suicidal ideation compared to women with no PMDD or PMS, while women with PMS were not in a risk for suicidal attempt [21]. Moreover, it is shown that women with PMDD appear to have an increased risk for comorbid attention deficit hyperactivity disorder (ADHD) [22], extending the criterion-symptom of “short attention span” and entering the field of a more generalized functional impairment.

Functional impairment. In the past, many studies evaluated the cognition in PMDD focusing on memory and attention, neglecting the functional part which refers to higher-order cognitive processes such as monitoring, organizing, flexibility, shifting, and planning [23]. At the same time there is also the view that it is not a matter of interest, but a matter of occupational competence that makes women with PMDD less functional during the luteal phase [24].

According to a 2022 study, women with PMDD exhibit reduced executive functioning during the late luteal phase. This impairment was associated with diminished use of cognitive reappraisal strategies (the ability to regulate emotions using logical patterns) and higher levels of depressive symptoms. Among the examined factors, inattention showed the strongest association with PMDD and with late-luteal-phase functional impairment, even after accounting for depressive symptoms [23]. These observations suggest that functional impairment is an inevitable part of the PMDD-symptom-complex concerning cognitive and emotional dimensions [17].

An Ecological Momentary Assessment study of 2020 highlights the exacerbation of symptoms during the late luteal (LL) phase as the distinguishing feature between PMDD and other

mood disorders. PMDD women report highest levels of rumination and lowest levels of self-acceptance during the late luteal phase, while healthy women do not show such cycle-dependent variations of mood and cognitions. Moreover, it was shown that PMDD is connected with a reciprocal relationship between rumination and NA, especially in the late luteal phase. However, the truly noteworthy finding of the study is that women suffering from PMDD tend to rumination as a response to negative affect independently from their cycle phase. Rumination appears as a constant characteristic of PMDD women compared to the non-affected ones [7], implying a stable functional impairment in terms of emotional control. Further studies have also indicated that PMDD is linked to avoidant personality disorder (for women above 30), impulsive-aggressive personality traits, depressive and manic symptoms independent of the menstrual cycle [20], probably due to the enhanced brain reactivity in the dorsal anterior cingulate cortex and dorsomedial prefrontal cortex [16].

Conclusions

In conclusion, PMDD appears as a result of multiple factors that may act, either as independent risk factors, or synergistically with one another. The disorder's pathophysiology is considered to reflect an impaired neural sensitivity to the endocrine fluctuations of the menstrual cycle [6], stemming from a problematic response to estradiol and progesterone. Serotonergic vulnerability [3], genetic predisposition [10], and exposure to stress and inflammation [7],[8],[9] could also play a significant role in the development of PMDD. Even anatomical variations have now been associated with PMDD symptomatology [11] [12].

Importantly, the clinical presentation that follows this pathophysiological pattern extends far beyond the typical premenstrual discomfort and it manifests as a broader pattern of functional impairment. The molecular mechanisms implicated in PMDD explain the disruption of overall functioning [23], supporting the view that PMDD

should not be considered merely a cycle-dependent mood disorder, but rather a condition characterized by permanent and multidimensional dysfunction [1].

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