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EDITORIAL

ARTIFICIAL INTELLIGENCE AND MEDICAL EDUCATION:

Ally or Enemy?

"The only way of discovering the limits of the possible is to go beyond them into the impossible."

— Arthur C. Clarke

In an era dominated by the cult of efficiency and objectivity and the liquid modernity of Zygmunt Bauman, medical teaching finds itself seduced by a technological mirage. The seductive glow of diagnostic algorithms, high-fidelity simulators, and the promise of standardized, infallible education echoes through the corridors of medical schools. It is the siren song revisited, promising to maximize learning and train "perfect" professionals. And while technology is an invaluable tool that enhances and complements, the obsession with it threatens to obliterate a fundamental truth: **medicine is an indivisible binomial of science and art.**

Science has given us a necessary course correction and a light amidst the ocean of information (much of it useless) published daily. With it, medical practice has abandoned obscurantism and embraced the precision of laboratory tests, the objectivity of radiology, and the rigor of evidence-based protocols. **Science is NECESSARY.** Medicine without science, today, is quackery. Today, a student can master the complexity of molecular biology in an app and virtually practice a surgery a thousand times without risk. These

are advances that save lives and elevate the quality of care. They are the robust and indispensable **skeleton** of medicine.

However, medicine is not just a skeleton. **Art is the soul that gives life to this structure**, the breath of humanity that transforms the technician into the healer. This art manifests in clinical intuition, a sixth sense that is refined with years of practice, in the subtlety of a question that uncovers the patient's true anguish. It is the ability to communicate a somber diagnosis with compassion and clarity, to touch a shoulder to convey relief, or to read anxiety in a family's eyes. The art of medicine cannot be programmed. **ART is the INDISPENSABLE FOUNDATION of medicine.** It is developed in the heat of human interaction, the uncertainty of the emergency room, and the intimacy of the consultation room.

The growing dependence on technology runs the risk of giving us a generation of professionals who are "super-scientists" but **emotionally illiterate**. Superheroes of diagnosis, but insensitive to pain. We may believe a haptic simulator can replicate the complexity of the human body, but it is incapable of emulating the complexity of the human soul. It does not teach how to deal with frustration, insecurity, or the crushing responsibility of holding a life in your hands. These lessons are not found in databases; they are forged in the fire of real experience.

Therefore, the role of formal education with experienced physicians is irreplaceable. The mentor is not a mere professor, but a moral guide, a guardian of tradition. It is they who teach that illness is only one part of the patient's story, and that effective treatment requires understanding the whole being. It is they who, during long nights on call, transmit the **ethics, resilience, and humanity** of the profession, showing how to navigate situations of uncertainty and how to cope with the suffering of others. Technology may be the lighthouse, but the wisdom of the master is the compass.

Ultimately, what is at stake is not the adoption of new tools, but the very essence of medicine. Technology is a powerful **ally**; it has its role and must be in the daily routines of medical school corridors and classrooms, but **never the protagonist**. It can enhance, but it can never replace formal education and the irreplaceable human experience.

We must find the balance, extracting the best from both worlds and always maintaining the focus that the target of the doctor's entire attention is still the **patient**, and not a cold, impersonal screen.

André Luis Alves DeLemos

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Editor

SUMMARY

International Edition Vol. I Nº 2

EXPEDIENT

EDITORIAL

SHORTS "Body Packing" as a cause of abdominal pain 08

Ronald Sérgio Pallota Filho

REVIEW ARTICLE Using artificial intelligence in clinical simulation activities 12

Andreia Maria dos Santos, José Roberto Generoso Júnior, Itamar Magalhães Gonçalves, Marcos Vianna Lacerda de Almeida, Leonardo Cavalcante, Núbia Cristina Freitas Maia, Carolina Felipe Soares Brandão

SISTEMATIC REVIEW Efficacy and safety of piribedil in the treatment of Parkinson's disease: Systematic review and meta-analysis. 20

Hernani Pinto de Lemos Junior, André Luís Alves de Lemos, Álvaro Nagib Atalah

ESSAY From Student to Clinical Thinker: How Experiential Learning Transforms Medical Education 36

Ronald Sérgio Pallota Filho

LITERATURE REVIEW Social Foundations and the Clinical Approach to Transgender Health Care 40

Jefferson Ferreira de França

REVIEW ARTICLE Surgical Sutures 48

Heraldo Inforzato

ESSAY Neurobiological and Evolutionary Bases of Human Behavior: The Birth of Morality and Ethics. 54

André Luis Alves DeLemos

ISSN 2965-17403
A BÚSSOLA
PERIÓDICO CIENTÍFICO

Shorts

This section is dedicated to the debate of relevant clinical cases that add value to general medical practice, in an objective and concise manner.

No data that could enable patient identification should be included in the case.

Please submit your contribution to: abussolaperiodico@gmail.com

Case Discussion submitted by Ronald Sérgio Pallota Filho, M.D.,Msc.

Case Report: "Body Packing" as a Cause of Abdominal Pain in a Young Immigrant

Case Presentation:

A 21-year-old male patient, a native of Bolivia, was admitted to the emergency department with diffuse and progressive abdominal pain that began 24 hours prior to arrival. He presented no other symptoms such as fever, nausea, or vomiting. On physical examination, the abdomen was notably distended and tympanitic. Bowel sounds (bruits) were present, and there were no signs of peritonitis.

To investigate the cause of the abdominal distension, a Computed Tomography (CT) scan of the abdomen was performed. The exam revealed the presence of multiple oval-shaped capsules with high density, scattered throughout the stomach, small intestine, and colon (Figures 1 and 2). The appearance of these structures was consistent with cocaine

capsules, indicating the patient was a "body packer"— a person who swallows drugs to transport them covertly.

The patient was hospitalized for clinical monitoring. Treatment included intravenous hydration, administration of analgesics for pain control, and the use of stimulant laxatives to aid in the elimination of the capsules. Following medication, the capsules were successfully eliminated, and the patient was discharged from the hospital without complications.

Discussion

Abdominal pain in young patients is a common clinical challenge, with a vast range of possible diagnoses. Frequent causes include gastroenteritis, appendicitis, cholecystitis, pancreatitis, renal colic, and intestinal obstruction (MURRAY et al., 2022; LONGO et al., 2019). In the presented case, the distension and presence of bowel sounds suggested an obstruction or distension, which directed the investigation toward a mechanical or functional cause.

The patient's origin—an area with illicit drug trafficking—raised suspicion for "body packing," especially because the initial symptoms were non-specific and the clinical history was limited (TRAUB; HOFFMAN; NELSON, 2003).

The Computed Tomography (CT) scan is the most effective imaging exam to confirm the diagnosis, as it allows visualization of the dense capsules along the gastrointestinal tract (SMITH; ROBERTS; JERRARD, 2018; PEREIRA et al., 2020). Rapid and accurate diagnosis is fundamental for conservative management, avoiding unnecessary surgical procedures and monitoring the risk of severe complications, such as capsule rupture and intoxication (TRAUB; HOFFMAN; NELSON, 2003).

This case highlights the importance of comprehensive clinical reasoning, the judicious use of complementary exams, and a multidisciplinary approach to ensure the safety and efficacy of treatment.

Conclusion

"Body packing," while not a common cause, must be considered in the differential diagnosis of abdominal pain in young people, especially in specific epidemiological contexts. Computed Tomography is an essential diagnostic tool. Careful clinical management and rigorous monitoring are crucial to prevent serious complications and ensure a safe discharge.

Informed Consent

The patient authorized the disclosure of clinical information and images for scientific purposes, guaranteeing anonymity, in compliance with current ethical standards.

Figura 1

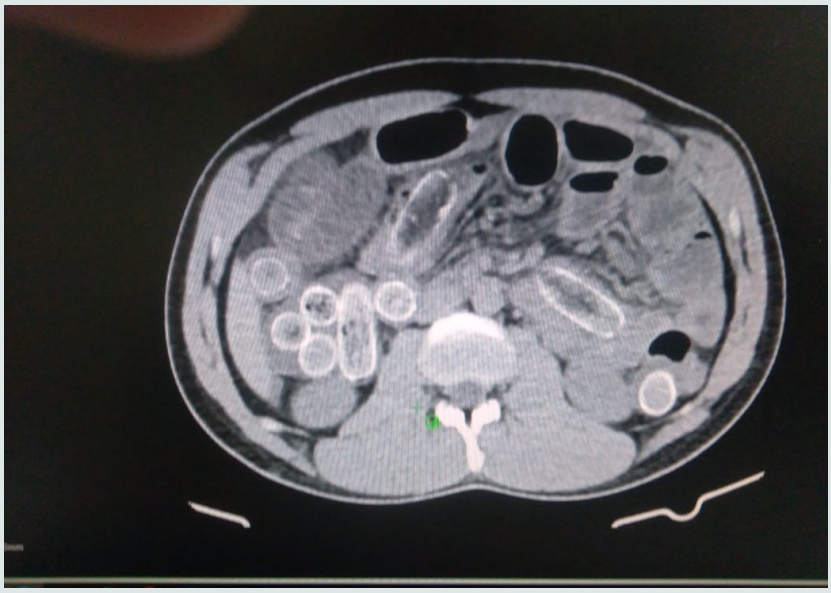


Figura 2

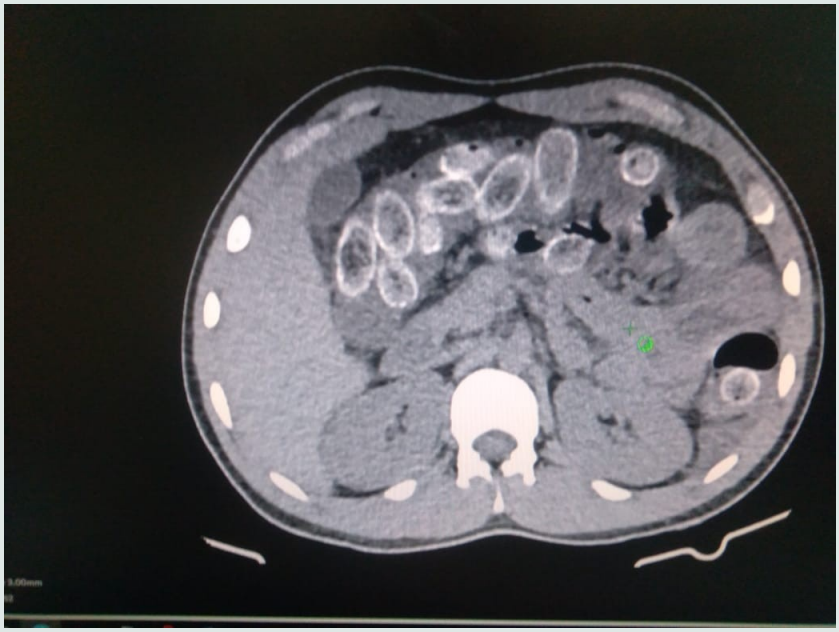
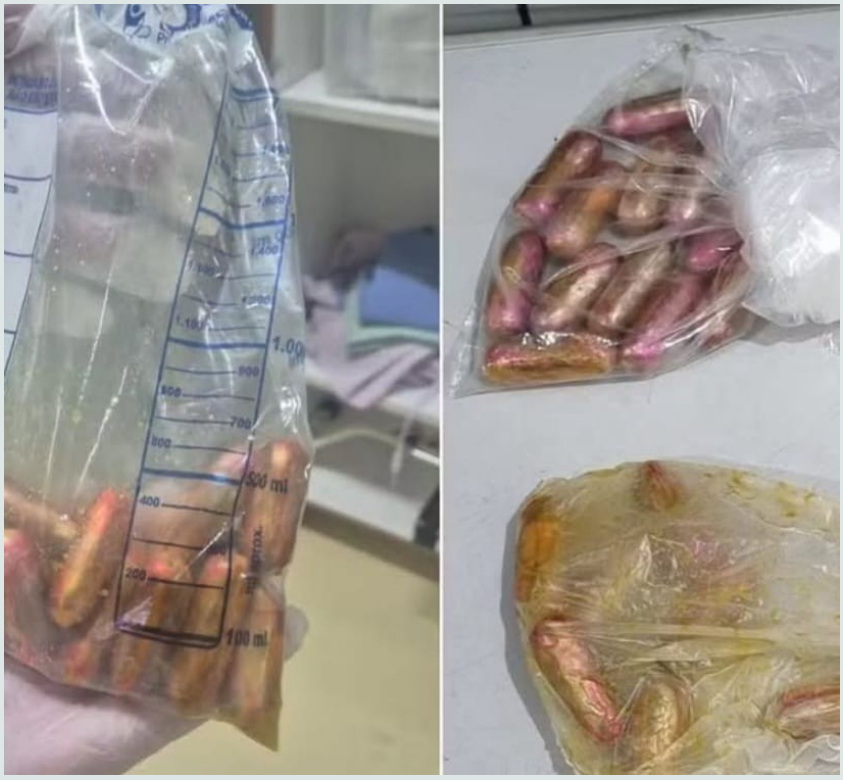


Figura 3



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Sobrassim
Sociedade Brasileira de Simulação na Saúde

REVIEW ARTICLE

Using artificial intelligence in clinical simulation activities.

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ABSTRACT

Objective: To analyze the relationship between Artificial Intelligence (AI) and clinical simulation, its applicability, challenges, and future proposals in the literature. Methodology: A comprehensive bibliographic search was carried out in the Medline (via PubMed), Embase, Scopus, ScienceDirect, and Web of Science databases, using subject descriptors in English, without any language restrictions, published in the last 5 years. Final considerations: There are still not enough studies dealing with high specificity on AI associated with simulation activities in the literature, even though it is a reality in the daily lives of professors worldwide. Apparently, the main use of AI at the moment is in the construction of simulation scenarios. Although it is already being used by professors due to its ease and practicality, further studies with rigorous validation are needed to corroborate its use in a valid and safe way. Undoubtedly, it promotes optimization of the complex process that is clinical simulation instructional design, as well as suggestions for bibliographies, debriefing style, and even student and professional evaluation techniques.

Keywords: Artificial intelligence; Medical education; Simulation; Simulation training.

INTRODUCTION In November 2022, an American technology company introduced ChatGPT to the world. This artificial intelligence (AI) software, known as a chatbot, is available free of charge in an online version, accessible to practically the entire world population. This program uses a question-and-answer format, classified as a "Generative Pre-trained Transformer (GPT)," a neural network model capable of learning complex language patterns that generate content[1]. Just a few weeks after its debut, ChatGPT generated considerable discussion across many sectors regarding its potential, including uses in health and education, as well as in simulation[1].

Artificial Intelligence (AI) represents an interdisciplinary field of computer science that seeks to develop systems capable of performing tasks normally associated with human intelligence, such as reasoning, learning, perception, and decision-making[2]. In recent years, AI has experienced rapid technological evolution, driven by significant advances in machine learning, deep learning, and big data processing. These advances have enabled the implementation of highly effective and specific solutions in various sectors, especially in the healthcare area[2].

In health education based on simulation, there are several potential uses for AI, including the creation of scenarios, the elaboration of learning objectives, the recommendation of equipment and resources, the structuring of debriefing points, and the provision of relevant references[1]. AI-based systems are capable of providing personalized scenarios, detailed performance analysis, and real-time feedback, which are fundamental aspects for maximizing the learning of students and health professionals[3].

Many AI tools have been used in medicine besides ChatGPT, such as Humata, WixADI, Revoicer, Synthesia, among others, which are selected depending on their functions, ranging from translators and content generators to scientific article summaries and other support tools. As these potentialities are already a reality, their function in simulation-based health education has evolved rapidly[1].

Given this development speed of AI, its growing presence in educational environments, including medical education, was already expected. Most Generation Z students seem more familiar and comfortable with integrating AI into their learning processes, often leveraging its benefits for productivity, personalization, and efficiency[4]. However, students and educators of all generations increasingly recognize both the potential and the limitations of using AI in education[4].

Artificial intelligence (AI) and its applications hold great promise for solving many of the global problems in healthcare, including making diagnoses, facilitating diagnoses, making decisions, analyzing big data, and general administration/management [5] [6]. AI has the potential to support the global shortage of medical specialists and expand access to healthcare in more remote areas[6].

Many fields of medicine have already benefited from the practical application of AI. Examples include the detection of atrial fibrillation, epilepsy, seizures, and hypoglycemia, or diagnoses of diseases based on histopathological examinations or medical imaging [6]. Recent data shows that all medical specialties are exploring the use of AI to assist doctors [7]. Deep learning algorithms can make functional sense of the growing amount of data used daily by individuals through wearables, smartphones, and other mobile monitoring sensors in different areas of medicine [7].

Among the most promising uses of AI in health simulation are the creation of highly realistic and interactive virtual patients, capable of responding dynamically to participants' actions. These virtual patients are developed using deep learning and natural language processing algorithms, allowing them to demonstrate emotions, complex clinical symptoms, and realistic verbal interactions, thus increasing the realism and educational effectiveness of the simulated scenarios [8].

Another relevant aspect is the use of AI for automatic performance analysis of participants during simulations. Advanced algorithms can accurately assess the procedures performed, identify errors or deviations from recommended clinical conduct, and provide instant and personalized feedback. This approach not only improves immediate learning but also facilitates the continuous development of professionals over time, through the identification of trends and specific areas for improvement [9].

Furthermore, AI has been used to predict clinical outcomes from simulations, allowing for the creation of preventive and early intervention scenarios in critical situations, such as medical emergencies, trauma, or complex surgical events. This predictive application contributes to better preparation of medical teams and potentially reduces real risks and complications in clinical practice[10].

This article aims to analyze the recent literature regarding the relationship between AI and clinical simulation, its applicability, challenges, and future proposals.

METHODOLOGY

A comprehensive bibliographic search was carried out in the Medline (via PubMed), Embase, Scopus, ScienceDirect, and Web of Science databases, using subject descriptors in English, without any language restrictions, published in the last 5 years (2021-2025). The descriptors used were: "Artificial Intelligence", "Medical Education", "Simulation" and "Simulation Training".

Content analysis was supported by the Rayyan software, which helped expedite the screening and selection of the most relevant studies and identify duplicate articles. Inclusion criteria were articles published in the last 5 years (2021-2025), without any language restriction. Exclusion criteria were bibliographic documents such as books, book chapters, theses, dissertations, and monographs, or subjects not correlated between AI and the use of clinical simulation. 2,055 related articles were located, of which only 12 articles met the inclusion criteria and were therefore selected for this review.

RESULTS

Table 1 below summarizes the articles selected in this review. It is noted that there is great agreement on the need to regularize AI as a member of curricular activities in a longitudinal manner, i.e., increasing its complexity. Basically, there are no studies that address AI and simulation activities with high specificity, with the exception of the articles in this table that address curricular integration and another on OSCE-style evaluation associated with AI (Objective Structured Clinical Examinations).

Year	Authors	Theme	Results
2025	Murat Tekin, et al	OSCE / IA.	AI proves promising as a supplementary tool for OSCE evaluation, especially for visual-based clinical skills
2024	Lukas Weidener et al	AI applications to students and ethical aspects.	Need for AI integration in medical schools as a clinical tool and ethical aspects in Switzerland, Germany, and Austria
2024	Atinc Tozsin,et al	The role of artificial intelligence in medical education: A systematic review.al Curricular insertion of artificial intelligence in medical education.	AI tools demonstrated effectiveness in enhancing practical skills, diagnosing diseases, and evaluating student performance. However, more research with rigorous validation is needed to identify the most effective AI tools for medical teaching.
2023	Jacob Krive et al	Curricular insertion of artificial intelligence in medical education.	Creation of a discipline that offers "literacy" about AI.
2023	Ali Jasem Buabbas, et al	Student perception of AI use.	Positive perceptions. There was a strong consensus that AI will not replace doctors but will drastically transform healthcare practices.
202	Li Sun, et al	Systematic review on	Suggestions on how AI curricular integration can occur. Need for

3		AI and COVID19.	regulation.
2023	Carl Preiksaitis	Opportunities, challenges, and future directions of AI in medical education.	Necessary to develop new skills and competencies related to AI, as well as thoughtful and differentiated approaches to examine the growing use of AI.
2023	Martin Tolsgaard, Martin V. Pusic, et al	The fundamentals of AI in medical education research.	Integrating learning sciences into the development and use of AI systems in healthcare will likely remain a challenge in the coming years.
2023	Jonny R. Varma	The global use of artificial intelligence in the undergraduate medical curriculum.	Results indicated that AI was used in a variety of specialties in undergraduate medical teaching and was used equally for pre-clinical and clinical periods.
2023	David L. Rodgers, et al	AI and the simulationists.	Consistency is still lacking in the responses originating from AI. Therefore, human intervention is currently necessary in the design of simulation scenarios using ChatGPT.
2022	M. Murat Civaner, et al	Artificial intelligence in medical education: a cross-sectional needs assessment.	Need for an update of the medical curriculum, according to the needs of the healthcare transformation driven by artificial intelligence.
2022	Joel Grunhut, et al	Needs, challenges, and applications of artificial intelligence in the medical education curriculum.	Longitudinal research plans are necessary to effectively study the best way to implement these curricular changes.

Source: Authors, 2025

DISCUSSION

Improving learning and reducing workload are no longer just promises of AI. However, concerns persist about over-reliance, ethical boundaries, and pedagogical suitability^1. As AI becomes more embedded in academic and professional environments, understanding it remains a critical area for exploration and investigation[3 4 5].

ChatGPT and AI as a whole learn based on what the user is asking and how they are formulating the question. With continuous questioning and requests for response reviews, the programs can provide increasingly useful information [6 7].

There are several limitations in ChatGPT, for example, as well as ethical controversies to be discussed. Reports have shown inaccuracies in the information provided by ChatGPT [6 7 8]. Articles reported that the accuracy of responses in more specialized areas, such as ophthalmology, showed more comprehension errors compared to general medicine topics, including difficulties in passing the written ACLS (Advanced Cardiovascular Life Support) exams of the American Heart Association [8].

However, the lessons learned so far about AI decision-making will apply to individuals across the healthcare spectrum, both in urban and rural settings, due to its potential to expand access to healthcare^6. Therefore, faculty and students must be prepared to learn about AI, regardless of the area of medicine they work in or choose [9].

Thus, the incorporation of AI in healthcare simulation represents a significant technological advance, expanding the scope and effectiveness of educational strategies and contributing to better clinical outcomes and patient safety. However, despite the clear opportunities, challenges related to validation, data security, and ethical and professional acceptance must be continuously evaluated and overcome to ensure the success of these implementations [12].

FINAL CONSIDERATIONS

Current and future advancements in AI in medicine require undergraduate medical and health educators to act and implement AI into their curricula. Longitudinal research plans are necessary to effectively study the best way to carry out these curricular changes. In the case of Brazil, a review of the National Curriculum Guidelines (DCNs) should be considered to regularize and further encourage institutional adaptation. The construction of simulation scenarios with AI is a reality that, although requiring review and studies to corroborate its use, greatly optimizes the complex process that is clinical simulation instructional design.

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Systematic review

Efficacy and safety of piribedil in the treatment of Parkinson's disease: Systematic review and meta-analysis.

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***Álvaro Nagib Atallah, MD, PhD. Full professor and Head of the Discipline of Emergency Medicine and Evidence-Based Medicine of Universidade Federal de São Paulo (Currently retired)— Director of the Brazilian Cochrane Center

Abstract

Introduction: Piribedil, a dopamine agonist, has been proposed as an alternative treatment for Parkinson's disease, offering good benefits and fewer side effects. Objectives: To verify the efficacy and safety of piribedil in the treatment of Parkinson's disease. Methods: Search strategy: a) Electronic: EMBASE, LILACS, MEDLINE, Cochrane Library. Selection criteria: a) Type of studies: All eligible, controlled, and randomized; b) Type of participants: Patients with Parkinson's disease; c) Intervention: Piribedil compared with placebo or another drug; d) Outcomes: Efficacy and safety. Data collection and analysis: Two reviewers independently reviewed the references found through the search strategy and applied the inclusion criteria to the selected studies. After all eligible studies were found, the data were summarized in a meta-analysis if two or more studies were included, or in an analysis if only one study was included. Results: Three studies were included in two comparisons: oral piribedil vs. placebo, and piribedil vs. bromocriptine. Analyses were performed in RevMan, with four meta-analyses showing detailed statistical significance for piribedil (vs. placebo) in the UPDRS II/III outcomes. The piribedil vs. bromocriptine comparison included only one study, and ten analyses were performed. Nine of them showed no statistical difference between the groups, and one showed a statistically significant difference favoring the bromocriptine group (hallucinations). Conclusion: This systematic review, based on the studies presented and the results, provides evidence of the effectiveness and safety of piribedil in the treatment of Parkinson's disease.

Keywords: Piribedil, Parkinson's disease, Dopamine agonist, Systematic review, Randomized clinical trials

1. Introduction

Parkinson's Disease

Parkinson's disease is characterized microscopically by the degeneration of dopaminergic neurons located in the brain, more specifically in the substantia nigra and the corpus striatum. The presynaptic terminals of dopaminergic neurons in this region undergo varying degrees of alteration, resulting in a lower level of dopamine synthesis and insufficient stimulation of the postsynaptic terminals for optimal neurotransmission. This degeneration compromises dopaminergic activity in the region, blocking or

promoting effective neurotransmission in the nigrostriatal pathway. Its etiology is likely multifactorial, and environmental, metabolic, and even genetic factors should be highlighted: the former due to the high prevalence of Parkinson's disease in industrialized areas or in regions where pesticides are used, with no specific evidence of a causal agent; the second, due to neurotoxicity caused by free radicals resulting from metabolic alterations, and the third is related to alterations in a specific locus on chromosome 4 observed in patients from the same family with Parkinson's disease. Clinically, this disease is characterized by rigidity of movement, accompanied by tremors of the extremities, which are most noticeable in the hands and face, an expressionless face, and progressive cognitive impairment. This allows Parkinson's disease to be diagnosed remotely in its more advanced stages.

The incidence of Parkinson's disease increases with age, and some data show a peak incidence between 70 and 79 years of age. The best studies estimate an incidence rate of approximately 17 per 100,000 per year[1]. The global average prevalence ranges from 57 to 271 per 100,000 population [2,3].

Dopamine

Dopamine is a chemical synthesized in dopaminergic neurons and stored in neuronal terminals. When a neuron is stimulated, dopamine is released into the synaptic cleft, binding to specific receptors, affecting neurotransmission, and then being either destroyed or reuptaken. There are two receptors, D1 and D2, each divided into subgroups: the first into D1 and D5, and the second into D2, D3, and D4. The dopaminergic pathways are the ascending system, which comprises the nigrostriatal pathway, the mesocortical pathway, and the mesolimbic pathway. The first, when affected, is responsible for motor disorders; the second is related to cognitive functions; and the third is related to memory, learning processes, and the regulation of affective behavior. The descending system includes the tuberoinfundibular pathway, which is related to neuroendocrine regulation.

Piribedil

Piribedil is a dopaminergic agonist, meaning it has the same activity as dopamine. There is a certain structural similarity between the dopamine molecule and piribedil. Furthermore, two piribedil metabolites exhibit dopaminergic activity in the D2 subgroup, albeit significantly lower than that of the parent molecule, yet still significant. Evidence of piribedil's dopaminergic activity was obtained in an experimental animal model. In this model, monkeys were subjected to a toxin (methylphenyltetrahydropyridine – MPTP) that specifically destroys dopaminergic neurons, chemically inducing Parkinson's disease. These animals exhibited signs similar to those observed in Parkinson's patients, including akinesia, rigidity, changes in motor coordination, and abnormal body movements and positions, but without a predominance of tremors, characteristic of the akinetic-hypertonic form of Parkinson's disease. In these monkeys, oral administration of piribedil improves motor coordination and reduces instability scores. When these animals were treated

with a peripheral dopaminergic antagonist (domperidone), which prevents gastrointestinal disturbances induced by dopaminergic agonists, the improvement induced by piribedil was even greater. After this animal experiment, the researchers reached the following conclusions regarding piribedil: 1ª. Piribedil acts not only on tremor, but on all motor signs of Parkinson's disease; 2ª. Among the dopaminergic agonists tested in animals, piribedil was the only one capable of increasing attention and alertness through its action on the mesolimbic and mesocortical dopaminergic pathways[4]. It was also found that when the specific binding of piribedil to dopaminergic brain structures is measured by the displacement of a marker (butaclamol), piribedil is capable of binding to dopaminergic structures, but not to non-dopaminergic structures[5]. Piribedil, like other dopamine agonists, reduces dopamine destruction in the rat brain, as demonstrated by microdialysis. This effect was assessed by the percentage of maximum inhibition of dopamine metabolite formation (DOPAC) and is marked in the limbic system (42%), frontal cortex (31%), and striatum (32%)[6].

2. Literature Review

Parkinson's disease is a progressive neurological disorder characterized by tremor, bradykinesia, rigidity, postural instability, and a variety of non-motor symptoms. While some signs and symptoms improve with levodopa, other axial signs, such as dysarthria, dysphagia, postural instability, rigidity, and most non-motor signs, such as depression, cognitive decline, and dysautonomia, typically do not respond satisfactorily to levodopa. Furthermore, levodopa use may be limited by the development of motor fluctuations, such as dyskinesias, and other adverse effects [7].

Since the introduction of dopamine replacement therapy using L-DOPA (l-3,4-dihydroxyphenylalanine) to treat Parkinson's disease, and the recognition of the problems associated with its use, numerous studies have investigated the regulation and function of the dopamine receptor in Parkinson's disease. These studies provide insight into the pathophysiological disorders and the consequences of chronic dopaminergic treatment, but they are ineffective in identifying new pharmacological targets or those as effective as L-DOPA for alleviating the symptoms of Parkinson's disease[8].

Dopamine agonists are highly effective as adjunctive therapy to levodopa in advanced Parkinson's disease and have rapidly gained popularity as monotherapy in the early stages of Parkinson's disease for patients around 65 to 70 years of age. In the latter case, dopamine agonists are approximately as effective as levodopa, and patients demonstrate a lower tendency to develop motor complications. However, dopamine agonists lose efficacy over time, and the number of patients remaining on monotherapy decreases to less than 50% after 3 years of treatment. Thus, after a few years of treatment, most patients who started on dopamine agonists will be treated with levodopa in a combined dopaminergic therapy to achieve better control of motor symptoms [9].

Complications with motor fluctuations and dyskinesias

Complications of long-term levodopa therapy, such as fluctuations in motor response and levodopa-induced dyskinesias, can become more debilitating than Parkinsonism itself and constitute a major problem in the pharmacological management of the disease[10]. Motor fluctuations include the "off" phenomenon (shortening of the period of clinical benefit induced by single doses of levodopa), on-off effects (sudden, random, and unpredictable loss of benefit during a successful phase induced by a single dose of levodopa that occurs before the expected "off" phase), and dyskinesias (involuntary twisting and turning movements). The medical term "on" refers to the time the medication provides benefit for mobility, slowness, and stiffness, and the term "off" refers to the period during which the medication no longer affects the same symptoms. In clinical practice, pharmacological treatment of motor complications is difficult. Recently, the results of large studies compared levodopa with different dopamine agonists [11,12,13,14] to decide on the initial treatment for patients recently diagnosed with Parkinson's disease, and demonstrated that the early use of dopamine agonists is effective in controlling Parkinsonian symptoms for more than three years and delays the occurrence of motor complications, when compared to treatment with levodopa. Several Cochrane systematic reviews [15,16,17,18], as well as a recent systematic review by the Movement Disorders Society[19], concluded that pharmacological treatments with dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors were effective for the treatment of motor fluctuations. A study with a rapidly dissolving formulation of selegiline, a monoamine oxidase (MAO) type B inhibitor, showed benefit in the treatment of motor complications[20].

Psychotic complications

Psychosis is a common, disabling, non-motor complication of Parkinson's disease (PD). It is defined as a disturbance of perception and thought and typically includes hallucinations, illusions, paranoid beliefs, agitation, and delirium. Drug-induced psychosis (DIP) can be a side effect of a single dose, even with early monotherapy with dopamine agonists or levodopa in new patients. In recent double-blind, placebo-controlled studies, an incidence of DIP of over 17% was reported in the first five years of treatment, even in an uncomplicated group of patients [21,22,23,24]. One study reported a prevalence rate of 40% when minor symptoms of psychosis, such as illusions or fleeting sensations of a person's presence, were included. The frequency of PD increases with disease progression and can occur in up to 70% of patients with dementia [25]. A variety of other risk factors have been associated with PD psychosis, including advanced age, brain atrophy, the presence and severity of depression, abnormal REM sleep regulation, early-stage dopaminergic drug doses, combination therapy, and high doses of anticholinergics [26-38]. The frequency of PD is higher with dopamine agonist treatment compared to levodopa monotherapy[39,40]. A systematic review suggests that the likelihood of hallucinations with agonists is more than twice that of levodopa alone[41]. Enhancing dopaminergic transmission by adding MAO-B inhibitors or COMT inhibitors can also occasionally

provoke psychotic symptoms, although these are rarely observed in clinical trials [42,43]. It is believed that anticholinergics may be more likely to induce IDP, particularly delirium, compared to amantadine [43].

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) may affect 20–50% of patients with Parkinson's disease (PD), whereas sleep attacks, which are episodes of sleep without prodromes, appear infrequent. EDS is associated with more advanced disease, higher doses of levodopa, and sometimes the use of dopamine agonists. Patients at risk for sleep attacks have higher Epworth sleepiness scores (ESS) (although a significant subset of patients have scores below this score). Polysomnography is a valuable tool in patients with PD, because sleep apnea can occur in 20% of patients. Removing or replacing a recently introduced dopamine agonist may offer some relief from EDS. Otherwise, the addition of modafinil has a benefit in patients with PD. EDS can also affect patients with atypical Parkinsonism, such as dementia with Lewy bodies and progressive supranuclear palsy[44].

A primary goal of research in Parkinson's disease (PD) is the discovery of new agents to improve symptomatic treatment. The aim of these new treatments should be to effectively control symptoms throughout the disease course without the development of motor side effects and psychiatric complications. Results from several clinical trials with new treatment options conducted in recent years have been negative or unsatisfactory. Most of the drugs and surgical procedures used in these studies were previously tested in monkeys and rats. They raise several questions about the true reality of animal studies, the adequacy of hypothesis-based clinical study design, the validity of current tools for assessing a specific effect, and the selectivity of the drugs used. All of these factors may explain the failure or partial success[45].

The pharmacological treatment of choice for the past 30 years has primarily been levodopa, a dopamine precursor. Although it is the most effective treatment available, it is clear that other drugs are needed to sustain therapeutic benefit and alleviate fluctuations in mobility (i.e., motor fluctuations). Furthermore, there is some evidence that levodopa may accelerate the occurrence of motor fluctuations and involuntary movements called dyskinesias. Consequently, many clinicians delay using levodopa and employ other symptomatic treatments, including monoamine oxidase type B (MAO-B) inhibitors and dopamine agonists, as first-line therapy in new patients. Despite treatment, the disease continues to progress as there is still no obvious way to alter disease progression (i.e., no neuroprotective therapy), restore dopamine loss (i.e., no restorative therapy), or prevent the disease (i.e., preventative therapy). As the disease progresses, polypharmacy is common and often employs a combination of antiparkinsonian agents. There have been some key advances in treatment with the advent of MAO-B inhibitors, dopamine agonists, and catechol-O-methyltransferase inhibitors, but the drug treatment arsenal remains limited. Modern drug treatments will continue to emerge in the preventive, reconstructive, and symptomatic areas

as new knowledge about disease mechanisms emerges. Regardless of the treatment purpose, the ideal pharmacologic drug for PD should include a safer, predictable side effect profile, a simple dosing regimen, the ability to provide symptomatic relief, and the potential to alter disease progression.

3. Methods

Study type: Systematic review of randomized clinical trials of piribedil compared with placebo or another drug in patients with Parkinson's disease regarding the following outcomes: change in the UPDRS (Unified Parkinson's Disease Rating Scale), motor disorders, cognitive disorders, and adverse effects.

Exclusion criteria: Clinical trials that did not meet the inclusion criteria. Study search strategy: Electronic search. All searches were conducted without language or date restrictions. The following databases were searched: Cochrane Library / MEDLINE / LILACS / EMBASE.

Search strategy:

(Piribedil) OR (Piribendyl) OR (ET-495) OR (ET 495) OR (ET495) OR (EU-4200) OR (EU 4200) OR (EU4200) OR (Piribedil Hydrochloride) OR (Hydrochloride, Piribedil) OR (Piribedil Mesylate) OR (Mesylate, Piribedil) OR (Piribedil Mono-hydrochloride) OR (Mono-hydrochloride, Piribedil) OR (Piribedil Mono hydrochloride) OR (Trivastal)

(Parkinson's Disease) OR (Idiopathic Parkinson Disease) OR (Idiopathic Parkinson's Disease) OR (Lewy Body Parkinson Disease) OR (Lewy Body Parkinson's Disease) OR (Paralysis Agitans) OR (Parkinson Disease, Idiopathic) OR (Parkinson's Disease) OR (Parkinson's Disease, Idiopathic) OR (Parkinson's Disease, Lewy Body) OR (Primary Parkinsonism) OR (Parkinsonism, Primary)

Study Selection

The selected studies were independently assessed twice using a standardized form and selected according to the inclusion criteria: study type, participant type, and intervention type. After reviewing the description of the allocation concealment process, the study was classified into four categories: a) allocation concealment was adequately reported (centralized randomization by an office or pharmacy; sequential administration of pre-coded or numbered packets to patients selected for the study; computerized system available 24/7 remotely; and other methods that provide adequate allocations, combined with the fact that the person who performed allocation concealment was not involved in its use); b) allocation concealment is not described, but the study is stated to be randomized. (lists or tables used; envelopes, but without specifying their type; an apparently adequate allocation, but with no other information in the study); C) means that allocation concealment was inadequate (alternation, date of birth, days of the week, any allocation concealment that is not completely unpredictable); D) means that the study is not randomized. Studies in categories A and B were selected. Another quality scale, Jadad, 1996,46 was also applied, assessing three factors that influence the internal validity of the study: a) was the study described as randomized? b) Was the study described as double-blind? c) Were losses to follow-up and patient withdrawals from the study described? Each item receives one point for a positive response, and one more point can be added or subtracted depending on the adequate description of the randomization or masking procedure. External validity was defined by the characteristics of the participants, interventions, outcomes studied, and methods.

Data Collection

Data were extracted independently by the two reviewers using a standardized form and cross-referenced to verify agreement. Discrepancies in results were resolved by consensus. To record the results of localized outcomes, another standardized form was used with specific locations for dichotomous and continuous data.

Analysis and Presentation of Results

Statistical analysis was performed using the Metaview module of the Review Manager [47] software, produced by the Cochrane Collaboration. For dichotomous variables, relative risk with a 95% confidence interval (random-effects model) was used. When there was a statistical difference, the number needed to treat (NNT) or the number needed to harm (NNH) was calculated. For continuous variables, the difference in weighted means (random-effects model) with a corresponding 95% confidence interval was calculated. If necessary, the original data were transformed to logarithmic bases for better distribution, or to scales with similar properties (data from this scale would be included in the meta-analysis). When necessary, continuous variables were subdivided for dichotomous analysis.

For sensitivity analysis, the following strategy was implemented: a) reanalysis of data with a reasonable variation in values for missing data: when extracting dichotomous variables, it was assumed that participants lost from the experimental group had treatment failure and that those lost from the control group had improved; b) reanalysis of data using a reasonable variation in the study results, when there was some uncertainty in the results; c) reanalysis of data using different statistical methods; d) statistical heterogeneity: in the studies,

it was planned to be assessed by inspecting the graphical presentation (scatterplot, in which the study weight or sample size was placed on the y-axis) against the risk ratio on the x-axis, and heterogeneity testing (chi-square test with N degrees of freedom, in which N is equal to the number of studies that contributed the data, minus one).

4. Results

1st study: Ziegler, 2003[48]: One hundred and fifteen patients participated in this randomized, double-blind, multicenter study, recruited from 31 centers in France and Portugal.

2nd study: Rascol, 2006[49]: 405 patients participated in this randomized, double-blind, multicenter study, recruited from 52 centers in seven countries (Argentina, India, France, Mexico, South Africa, Spain, and Portugal).

These two studies compared piribedil versus placebo administered orally. The following outcomes were common to both studies, providing data for the meta-analysis:

Figure 1. Meta-analysis representing the outcome of improvement in UPDRS II/III scores.

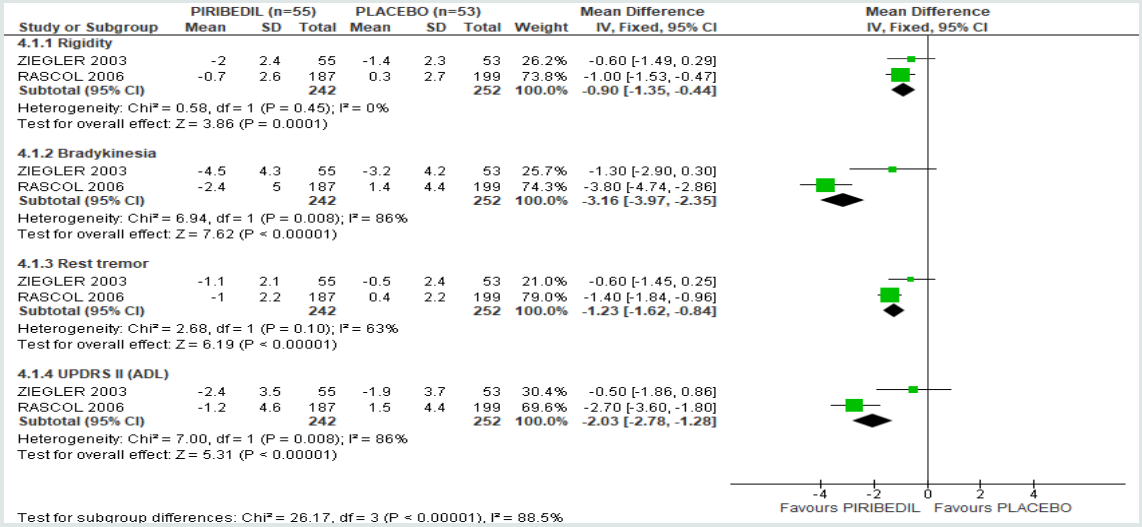
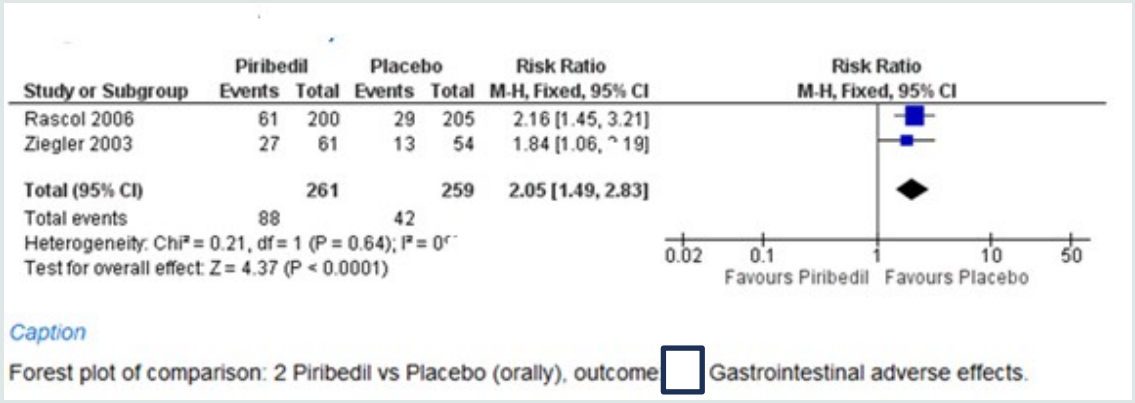


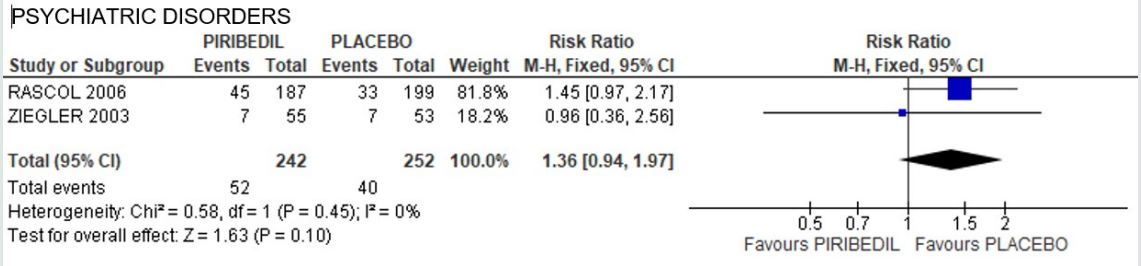
Figure 1 compares four outcomes that are common to both studies, showing four meta-analyses that are statistically favorable to piribedil.

Figure 2. Gastrointestinal adverse effects.



In Figure 2, in the gastrointestinal adverse effects outcome, the meta-analysis shows statistical significance for the placebo group with a confidence interval of 1.49 to 2.83, relative risk of 2.05, risk difference of 17, and number needed to cause harm (NNH) of 6, that is, only 1 patient in every 6 treated with piribedil does not present gastrointestinal problems.

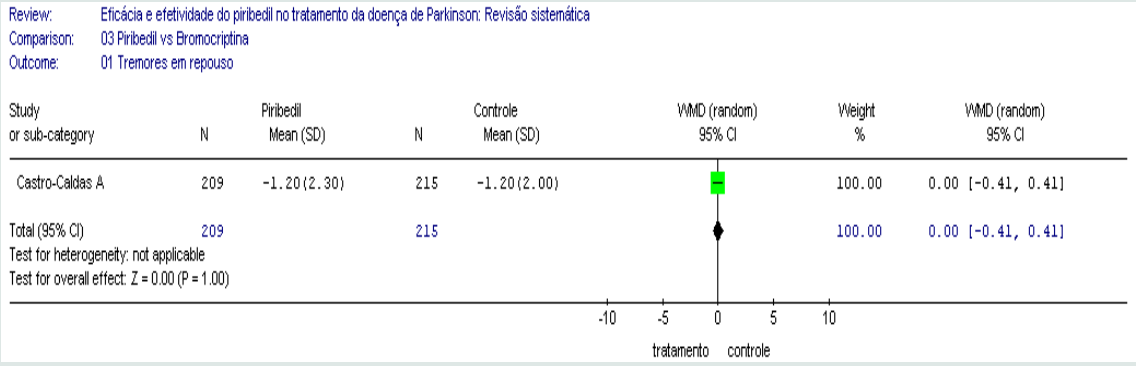
Figure 3. Graph representing the outcome of psychiatric disorders.

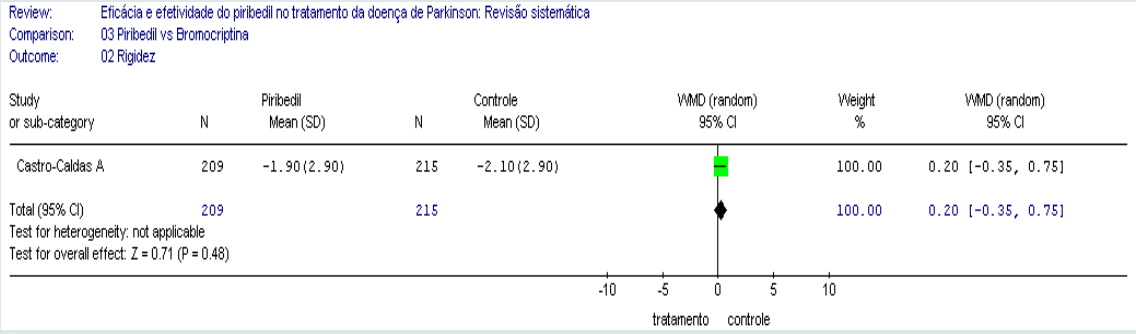


In Figure 3, the meta-analysis on the outcome of psychiatric disorders shows no statistical difference between the piribedil and placebo groups, with a confidence interval (CI) of 0.94, 1.97, relative risk of 1.36.

3rd study: Castro-Caldas, 2006[50]. This international clinical trial (8 countries) used a randomized, double-blind, parallel design, lasting 12 months, and aimed to evaluate the efficacy of piribedil 150 mg versus bromocriptine 25 mg. In this comparison, piribedil versus bromocriptine, we have only one study with the following outcomes analyzed:

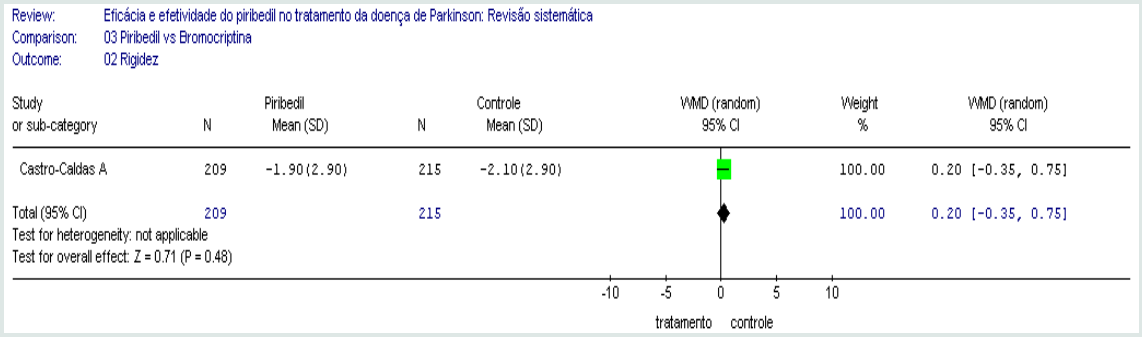
Figure 4. Graph representing the outcome of resting tremors in the comparison of piribedil versus bromocriptine.





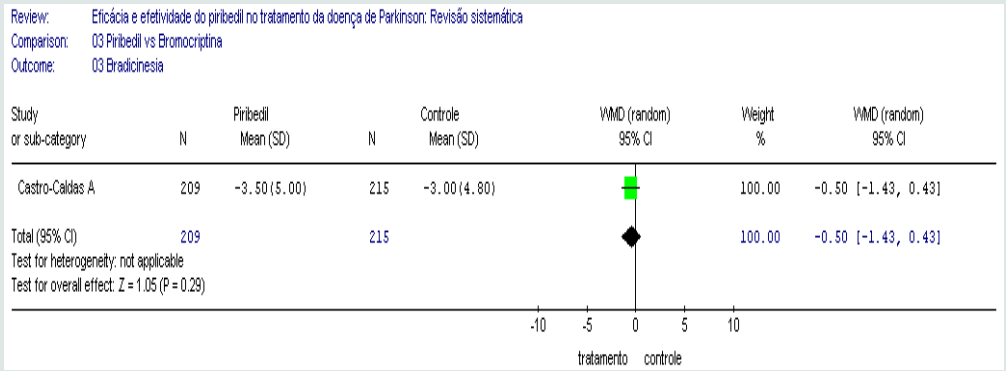
When comparing piribedil with bromocriptine, there was no statistical significance in the outcome of tremors at rest for either group, CI = -0.41, +0.41.

Figure 5. Piribedil vs Bromocriptine: Rigidity



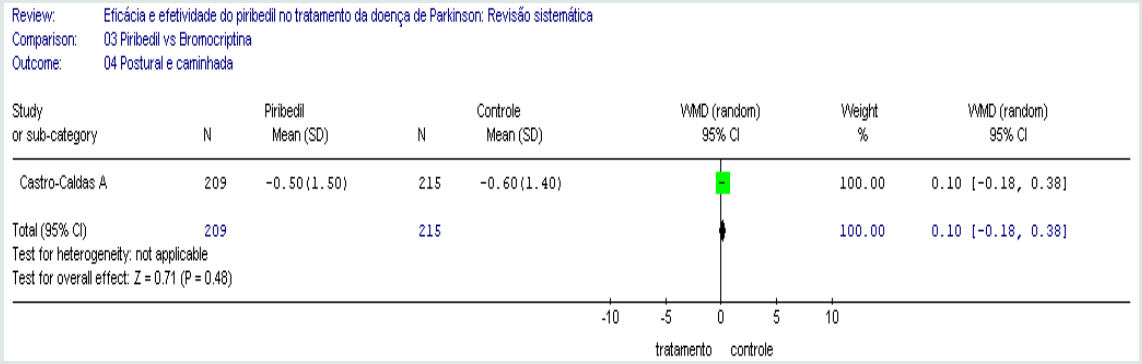
In the rigidity outcome, there was no statistical significance between the groups, CI= -0.35, 0.75.

Figure 6. Graph representing the bradykinesia stage.



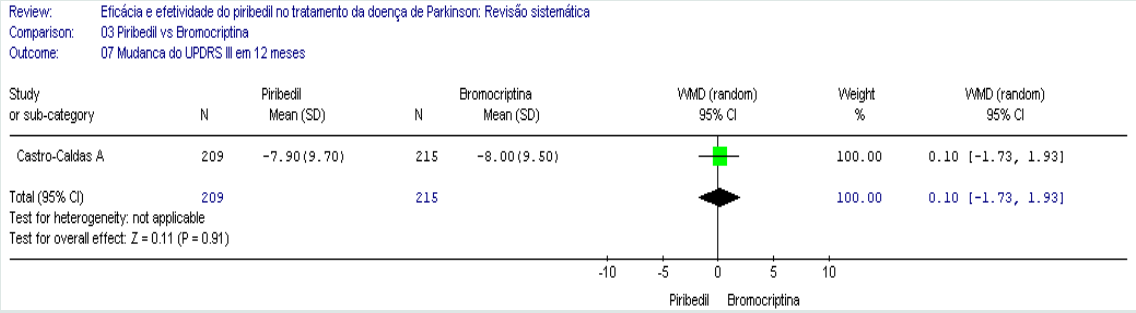
In the bradykinesia outcome, there was no statistical significance between the piribedil and bromocriptine groups.

Figure 7. Graph representing postural and walking outcomes.



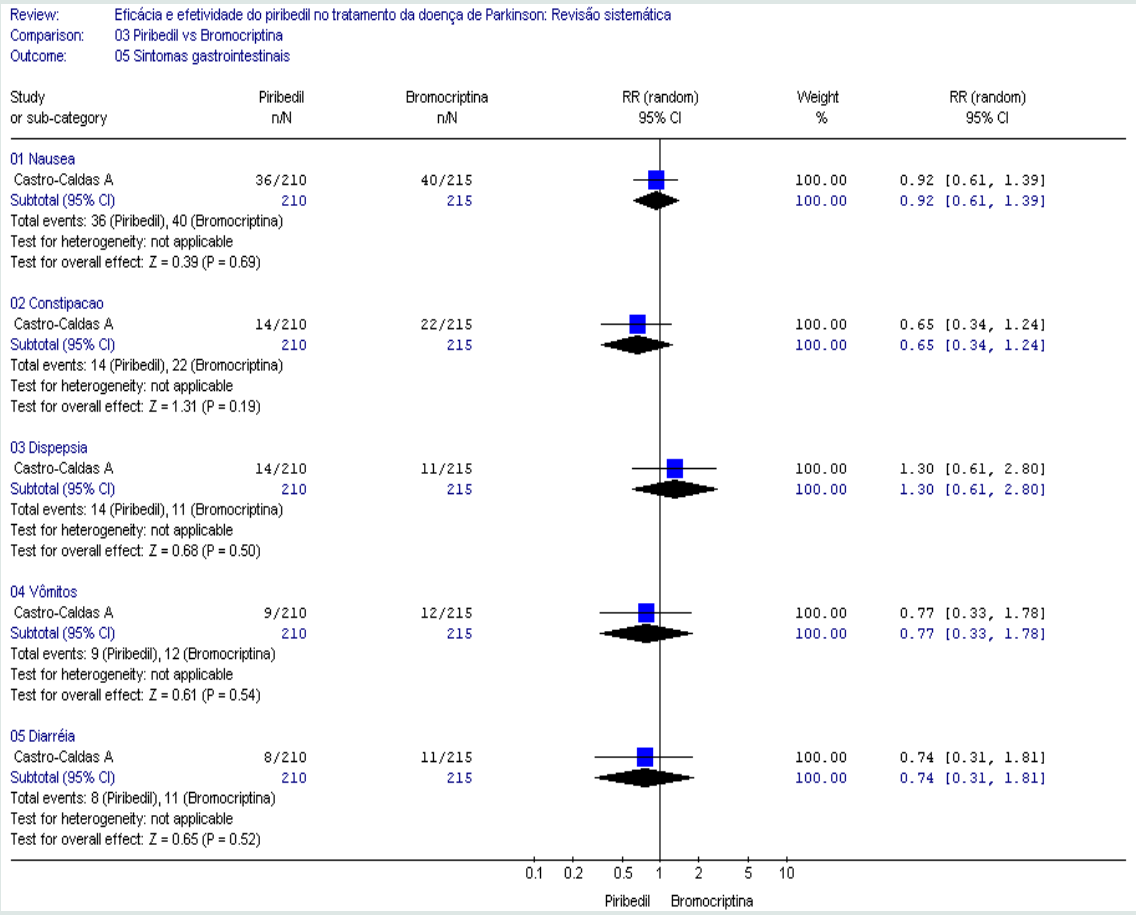
In the postural and walking outcome, there was no statistical difference between the postural and walking groups, CI = -0.18, 0.38.

Figure 8. Graph representing the outcome of the change in UPDRS III in 12 months.



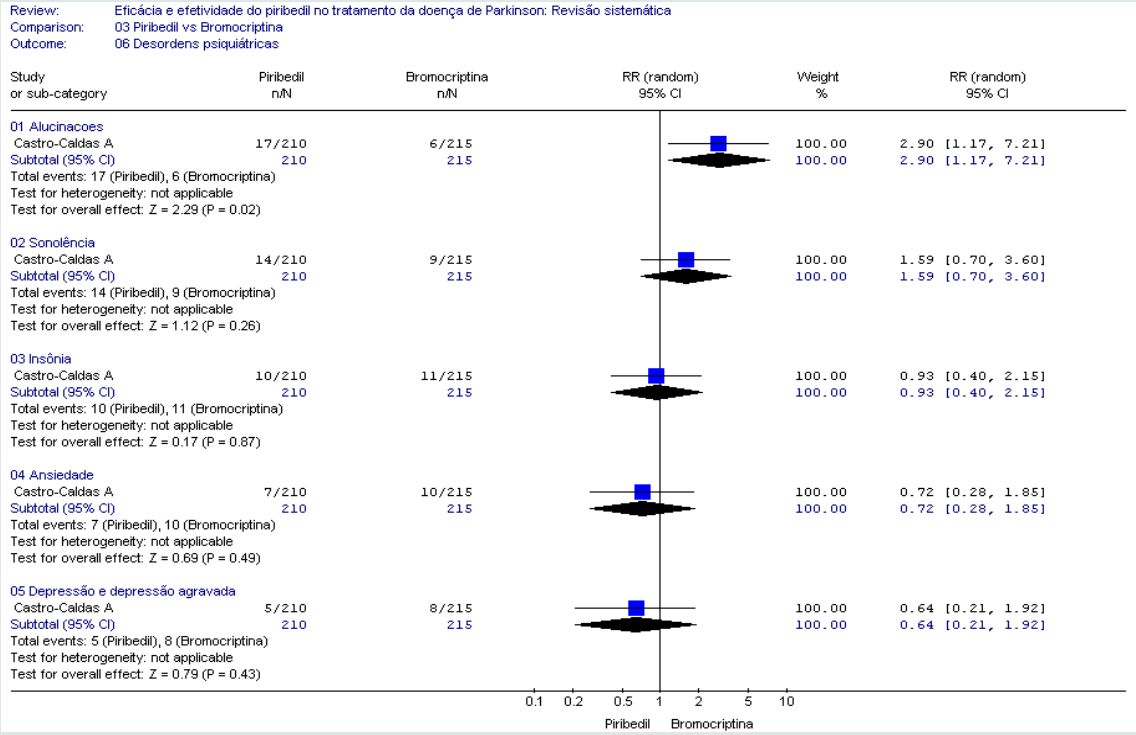
In the outcome of UPDRS change at 12 months, there was no statistical difference when comparing piribedil and bromocriptine.

Figure 9. Graph representing the outcome of gastrointestinal adverse events.



In the outcome of gastrointestinal adverse events, five symptoms and signs were evaluated (nausea, vomiting, dyspepsia, diarrhea, and constipation) between the piribedil and bromocriptine groups, and there was no statistical significance in any of the subevents.

Figure 10. Graph representing the outcome of psychiatric disorders between the piribedil and bromocriptine groups.



In the analysis of psychiatric disorder outcomes, five comparisons were made between piribedil and bromocriptine. Of these, four outcomes—insomnia, somnolence, depression, and anxiety—showed no statistically significant differences between the groups. However, for the outcome related to hallucinations, there was a statistically significant advantage for the bromocriptine group. The confidence interval for this result was +1.17 to +7.21, with a relative risk of 2.90.

5. Discussion

In the placebo vs. orally administered piribedil comparison, two studies [48,49] analyzed the outcomes of improvement in UPDRS II/III (four meta-analyses), gastrointestinal adverse effects, and psychiatric disorders. The first four meta-analyses were all favorable to piribedil (Figure 1), with statistical significance. The fifth meta-analysis (Figure 2) on gastrointestinal adverse events showed broad statistical significance in favor of placebo, highlighting the deleterious peripheral dopaminergic action of piribedil on

the gastrointestinal tract, which can be mitigated with the use of ondansetron hydrochloride, a potent, highly selective 5-HT3 receptor antagonist. It is important to remember that the dopaminergic action on the digestive tract was already expected, and this meta-analysis demonstrated what already exists in the literature. The sixth meta-analysis (Figure 3), psychiatric disorders, showed no statistical significance for any group. It was also expected, in the placebo comparison, that the dopamine agonist piribedil would produce more psychiatric disorders than placebo, as the literature shows a high incidence of this outcome, which increases with increasing disease duration and with the use of dopamine agonists [21-25;39-41]. This outcome, without statistical significance, contrasts with the literature, and it can be inferred that the study time was too short to evaluate this outcome.

The other adverse events were cited in both studies and analyzed without statistically significant differences, so it was decided not to present the graphs.

In the second comparison included in this systematic review, piribedil vs. bromocriptine, only one study50 provided the analyzed outcomes, and no meta-analysis was possible. All of the analyses yielded results without statistical significance for any group, except for the hallucinations subgroup in the psychiatric disorders outcome, which favored bromocriptine (Figure 10). In this comparison, unlike the previous comparison which included an active and passive drug, it was decided to present all analyses because the two medications in use are active but pharmacologically different. Both are dopamine agonists, but bromocriptine is an ergoline derivative, whereas piribedil is not.

A study conducted in Germany aimed to investigate the effects of piribedil on vigilance and cognitive performance in patients with Parkinson's disease who experienced excessive daytime sleepiness while taking pramipexole or ropinirole. The study was randomized, active-controlled, and blinded for assessors, lasting 11 weeks; eligible patients (N=80) were randomly assigned to receive piribedil or continue with pramipexole or ropinirole. The primary outcome was the Test Battery for Attention Performance (TAP), and secondary outcomes included the Epworth Sleepiness Scale (ESS) and the Unified Parkinson's Disease Rating Scale (UPDRS). This study demonstrated that switching from pramipexole or ropinirole to piribedil did not affect the primary outcome of the TAP or the secondary outcome of the UPDRS III. Piribedil reduced excessive daytime sleepiness, with lower ESS scores at the end of treatment compared to pramipexole or ropinirole (-4 vs. -2 points; P = 0.01). This study demonstrated equivalence between piribedil and pramipexole or ropinirole on two important outcomes, but showed superiority on the ESS. By not separating the two drugs compared with piribedil, this article missed the opportunity to narrow down which of them contributed or not to piribedil's superiority on the ESS. If the studies had been conducted separately, piribedil versus ropinirole and piribedil versus pramipexole, there would have been two analyses and more contributions to the difficult art of drug selection[51].

In China, a systematic review of randomized controlled trials (RCTs) was conducted comparing two non-ergoline dopamine agonists, piribedil and pramipexole, in the treatment of early-stage Parkinson's disease. Finding no RCTs comparing piribedil and pramipexole, they searched for studies comparing each with placebo and analyzed the results for the desired outcomes. Six trials provided data for pramipexole versus placebo, and two compared piribedil versus placebo, facilitating indirect comparisons. No significant differences were found between pramipexole and piribedil regarding change in UPDRS score from baseline. Piribedil and pramipexole demonstrated superiority over placebo for change in UPDRS II/III scores at weeks 22 to 30. No significant differences were observed between treatments at weeks 20 to 35 for anxiety, constipation, hypotension, nausea, and somnolence. This systematic review used extensive statistical resources to reach these conclusions, but it cannot convince everyone. Eight RCTs were conducted by different study groups, different locations, different individuals with different comorbidities, and different numbers of participants to compare data from six studies of pramipexole versus placebo with two studies of piribedil versus placebo[52].

Therefore, given the results presented, there is a discrepancy with the pharmacology of piribedil promoted in animal studies and non-randomized studies. The issue cannot be resolved because the studies presented in this review were not unanimous in their intervention and comparisons, as well as in the follow-up time and presentation of outcome results. However, given the importance of a systematic review that seeks studies with high methodological quality, piribedil and other dopamine agonist drugs cannot be promoted as priorities in the treatment of Parkinson's disease. They can and should be used with strict individualized medical monitoring.

6. Conclusion

In this systematic review, we found evidence of the effectiveness and safety of piribedil in the treatment of Parkinson's disease in the included studies.

Implications for Research

It is unbelievable that drugs that have existed for decades have been rejected in multicenter studies with good methodological quality. All drugs, whether new or not, should be tested against each other so that the decision to use them is based on evidence and not on pharmacological or commercial recommendations.

Implications for Practice

Until further studies are conducted, piribedil, according to the results of this systematic review, can be used in the treatment of early Parkinson's disease or as an adjunct to levodopa.

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Essay

From Student to Clinical Thinker: How Experiential Learning Transforms Medical Education

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Abstract

Contemporary medical education demands the acquisition of competencies that transcend technical knowledge, emphasizing the development of clinical reasoning and critical reflection. David Kolb's Theory of Experiential Learning proposes a dynamic cycle of experience, reflection, conceptualization, and experimentation that facilitates the construction of practical and adaptive knowledge. This theoretical-reflective essay analyzes the formative potential of this approach in the transition from student to clinical thinker, highlighting the importance of faculty mediation and the integration between intuitive and analytical cognitive processes. The results indicate that experiential learning constitutes a robust epistemological and pedagogical matrix for medical education, favoring the construction of cognitive, emotional, and ethical competencies essential to clinical practice. Finally, the essay discusses the need for curriculum reformulation and teaching strategies that promote authentic, reflective, and participatory learning environments.

Keywords: Experiential Learning; Clinical Reasoning; Medical Education; Medical Training; Critical Thinking.

Introduction

Medical education faces significant contemporary challenges in training professionals capable of dealing with the complexity and uncertainty of clinical care. In a scenario marked by rapid technological advances and information overload, it becomes essential that teaching goes beyond the simple transmission of content and incorporates methodologies that develop superior cognitive skills, among them clinical reasoning. The Theory of Experiential Learning, proposed by Kolb (1984), founded on thinkers such as Dewey, Piaget, and Lewin, presents itself as a model capable of integrating practical experience, reflection, and theory, promoting deep and contextualized learning. This article proposes a critical reflection on how experiential learning can transform the

medical training process, encouraging the transition from student to the role of clinical thinker.

Objectives

This work aims to analyze the role of experiential learning in the development of clinical reasoning in medical students during the clinical cycle, discussing its pedagogical implications and its articulation with contemporary theories of clinical thinking and faculty performance.

Methodology

This is a theoretical-reflective essay based on a narrative review of the literature pertinent to medical education and cognitive sciences. Kolb's (1984) concepts on experiential learning, Schön's (1983) principles of reflection-in-action, Bruner's (1999) contributions on the culture of education, Kahneman's (2012) dual-process theory, and Norman and Eva's (2005; 2010) analyses of clinical reasoning were used as the theoretical basis, complemented by the critical perspective of Paulo Freire (1987). The analysis articulated these contributions to identify how experiential learning can favor the development of reflective and autonomous clinical thinking.

Results

The theoretical-reflective synthesis demonstrated that experiential learning constitutes a robust pedagogical structure for the development of clinical reasoning. Kolb's proposed cycle, involving concrete experience, reflective observation, abstract conceptualization, and active experimentation, provides students with systematic opportunities to integrate practical experiences and critical reflection, an essential condition for developing complex clinical competencies. The importance of faculty mediation is highlighted in creating safe environments that stimulate student autonomy, allow learning through error, and promote the articulation between intuitive and analytical cognitive processes. The incorporation of critical education perspectives, especially those proposed by Freire, broadens the understanding of training clinical subjects capable of interpreting contexts,

questioning paradigms, and acting with ethics and responsibility. The findings indicate that, beyond exposure to care, the development of clinical thinking requires the active promotion of reflection and dialogue, integrating theory and practice in a continuous movement of knowledge reconstruction.

Discussion

The experiential learning model presents itself as an effective alternative for teaching clinical reasoning, as it values lived experience as the primary source of knowledge and favors the development of metacognition and critical judgment. Schön (1983) reinforces this idea by emphasizing reflection-in-action, a skill that distinguishes the competent professional and can be cultivated in the learning environment. Kahneman's (2012) dual-process theory complements this view by explaining how clinical reasoning integrates intuitive and analytical modes, which can be refined through reflective repetition and supervised practice. Norman and Eva (2010) draw attention to the need for educational environments that stimulate the fluidity between these systems, a condition provided by Kolb's experiential cycle.

In pedagogical practice, the professor assumes the role of mediator and facilitator, moving away from the traditional model of knowledge transmitter. From the Freirean perspective (1987), the faculty must promote the dialogical construction of knowledge, valuing active student participation and recognizing them as historical subjects. This role is fundamental for developing clinical competencies, as it allows for the personalization of teaching according to individual learning styles (Kolb & Kolb, 2005) and the stimulation of cognitive autonomy.

Critical reflection and engagement with experience enable the student to transcend simple content memorization, adopting an investigative and ethical posture toward care. Thus, experiential learning not only enhances clinical reasoning but also strengthens professional identity, human sensitivity, and social commitment.

Conclusion

Experiential learning is revealed as an essential epistemological and pedagogical matrix for contemporary medical training, as it dynamically and dialogically integrates theory, practice, and reflection. By favoring the transition from student to clinical thinker, this approach demands a repositioning of teaching practices and the curriculum, prioritizing authentic experiences, reflective spaces, and qualified mediation. Investing in the training of the professor as a facilitator of the experiential cycle is a *sine qua non* condition for consolidating this transformation, contributing to the training of critical, reflective, and committed physicians dedicated to the complexity of health care.

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Literature Review

Social Foundations and the Clinical Approach to Transgender Health Care

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Health care directed at transgender people must be understood within the scope of an expanded perspective, based on the principles of comprehensiveness, equity, and universality of the Unified Health System (SUS). This care should not be restricted to the biomedical dimension but must consider the social determinants of health, the promotion of human rights, and the valorization of gender diversity as a legitimate expression of human experience, breaking with cisnormative, heteronormative, and pathologizing models that have historically marginalized this population [1,2].

Historically, health assistance for trans people has been associated with pathologizing models that linked transgender identity to mental disorders. For many years, transsexualism was classified as a mental disorder in diagnostic manuals, such as the DSM (Diagnostic and Statistical Manual of Mental Disorders) and the International Classification of Diseases (ICD) of the World Health Organization (WHO). The most recent revision, ICD-11, published in 2019, represented a milestone by removing transsexualism from the mental disorders section and reallocating it to the category of conditions related to sexual health, under the term "gender incongruence," reinforcing an understanding based on human rights, self-determination, and depathologization [3,4].

Even with regulatory advances, structural, institutional, and symbolic barriers persist in clinical practice that limit transgender people's access to health services. This population presents higher rates of depression, anxiety, suicidal ideation, and attempts, substance abuse, sexually transmitted infections, including HIV, in addition to complications associated with hormonal self-medication, which is often performed without adequate monitoring [5,6]. Such outcomes are directly related to social determinants, especially structural violence, discrimination, exclusion from educational spaces and the labor market, food insecurity, and difficulty accessing housing and health care [7,8].

Intersectionality is essential for understanding how the oppressions of gender, race, class, territory, and disability intersect, aggravating conditions of social and health vulnerability. In Brazil, being a Black trans person, living in a periphery, and in a situation of poverty represents the intersection of multiple axes of oppression, generating inequalities in all spheres of life, including access and permanence in health services [8,9].

Appropriate clinical practice for transgender people must be anchored in the principles of accueil (welcoming), comprehensiveness of care, and strengthening of autonomy, based on qualified, empathetic, and non-judgmental listening. The correct use of the social name, pronouns, and the recognition of gender identity is a fundamental element for building the therapeutic bond and, more than an administrative act, constitutes a strategy for promoting mental health and well-being [1,5,10].

Cross-Sex Hormone Therapy: Transfeminine People

Among the main health demands of this population, cross-sex hormone therapy stands out, which consists of administering secondary sex hormones to align bodily characteristics with the gender with which the person identifies. This process must be conducted based on informed consent, individualized analysis of risks and benefits, evaluation of clinical conditions, and continuous monitoring, as advocated by the guidelines of the World Professional Association for Transgender Health (WPATH), in its eighth version, and the Endocrine Society [11,12].

In the case of transfeminine people, hormone therapy involves the use of estrogens, alone or in combination with antiandrogens. Estrogens are responsible for body fat redistribution, breast development, reduced muscle mass, and decreased hair growth (pilosity). However, their use is not without risks, especially venous thromboembolism, whose incidence is higher when synthetic estrogens, such as ethinyl estradiol (present in oral contraceptives), are used—a substance expressly contraindicated in this context [11,13]. Best practices indicate the use of bioidentical estrogens, preferably via transdermal or parenteral routes, reducing associated risks, especially in individuals with cardiovascular risk factors or those over 45 years of age [12].

Estrogen Formulations and Dosages (Transfeminine)

Various estrogen formulations are used in the hormone therapy of trans women and transfeminine people. Among the main ones is 17β-estradiol (or bioidentical estradiol), which can be administered orally (PO), at a dosage of 1 to 6 mg daily. Usual doses vary between 4 mg daily without the use of an antiandrogen and 2 to 4 mg daily when used in association with antiandrogenic agents. The dose should preferably be divided into two daily intakes, with a maximum of 2 mg per time [20].

Another widely used oral formulation is estradiol valerate, also at a dosage of 1 to 6 mg/day. Usual doses follow the same pattern as bioidentical estradiol: 4 mg/day without an antiandrogen or 2 to 4 mg/day with concomitant antiandrogen [20].

Regarding topical formulations, estradiol hemihydrate in gel (0.6 mg/g) can be administered through different dosing devices: 1 to 2 doses (ruler) of 1.5 mg/day; 2 to 4 doses (pumps) of 0.75 mg/day; or 3 to 6 doses (metered pump) of 0.5 mg/day. Usual doses are 2 daily doses, whether by ruler or pump. Application should be performed on the thigh, abdomen, or lower back on clean, dry skin, waiting for complete drying before contact with clothing or other materials [20].

Finally, 17β-estradiol in gel (available in 0.5 mg or 1 mg sachets) is administered via the topical route, with a dosage of 0.5 to 2 mg/day. The usual dose is 1 mg daily. The application follows the same precautions as the previous formulation, to be applied to clean, dry skin, with adequate drying time before contact with fabrics [20].

Antiandrogens

Antiandrogens, such as cyproterone acetate and spironolactone, are used to reduce testosterone levels, favoring the emergence and maintenance of desired secondary sexual characteristics. However, cyproterone, while effective, is associated with important adverse effects, such as hepatotoxicity, elevated prolactin, development of prolactinomas, and, with prolonged use, increased risk of meningiomas [11,14]. Studies show that lower doses of cyproterone, between 10 and 25 mg/day, can be equally effective in reducing serum testosterone levels, presenting a lower risk of adverse effects compared to traditionally higher doses [15].

Injectable and Transdermal Estrogen Alternatives

Injectable estradiol valerate (10 mg/mL), for intramuscular (IM) administration, is usually prescribed at a dosage of 10 mg every 4, 2, or 1 week, with 20 mg every 4 weeks being the typical maintenance dose in individuals not using antiandrogens. This formulation is difficult to find alone in the Brazilian market, being more accessible through pharmaceutical compounding. Estradiol valerate is often associated with norethisterone enanthate, although this combination is not widely recommended in the context of trans hormone therapy due to the cardiovascular risk associated with the synthetic progestogen [20].

Another available alternative is the transdermal estradiol hemihydrate patch. Available in presentations of 25, 50, 100, or 200 micrograms, it is used every 3 to 4 days, with a usual dose of 50 mcg twice a week. This formulation has the advantage of maintaining more stable serum levels, reducing hormonal peaks and their associated adverse effects. It is

especially indicated for patients with contraindications to the oral route or injectable estrogens [20].

Timeline of Effects (Transfeminine)

Effect	Onset	Maximum Effect
Fat Redistribution	3 to 6 months	2 to 5 years
Reduced Muscle Mass/Strength	3 to 6 months	1 to 2 years
Skin Softening/Reduced Oiliness	3 to 6 months	Time until maximum effect is unknown
Reduced Libido	1 to 3 months	1 to 2 years (stabilization)
Reduced Spontaneous Erections	1 to 3 months	3 to 6 months (significant reduction/disappearance)
Breast Growth	3 to 6 months	2 to 3 years (peak)
Reduced Testicular Volume	3 to 6 months	2 to 3 years
Body/Facial Hair Reduction	6 to 12 months	> 3 years (significant reduction)
Reduced Energy (Mental/Physical)	1 to 3 months	Time until maximum effect is undefined

Cross-Sex Hormone Therapy: Transmasculine People

For transmasculine people, the hormone therapy process is carried out with the administration of testosterone, generally in injectable formulations of cypionate, enanthate, or undecanoate testosterone, in addition to transdermal options. Expected effects include voice deepening, facial and body hair growth, clitoral hypertrophy, body fat redistribution, cessation of menstruation, increased muscle mass, and increased libido [11,12].

Although testosterone presents significant benefits for aligning gender expression, it can also generate adverse effects, such as increased hemoglobin and hematocrit levels (risk

of polycythemia), changes in lipid profile, acne, androgenic alopecia, and persistent pelvic pain, requiring regular monitoring [16]. Despite potential impacts on the lipid profile, current literature does not demonstrate a significant increase in the incidence of cardiovascular events in trans men using testosterone, provided there is adequate clinical monitoring [16,17].

Testosterone Formulations and Dosages (Transmasculine)

Formulation	Route	Standard Dosage	Key Characteristic
Testosterone Undecanoate (250 mg/mL)	Intramuscular (IM) Depot	1000 mg every 90 days	Promotes stable serum levels; not ideal for initial phase (due to long action).
Testosterone Cypionate (100 mg/mL)	Intramuscular (IM)	200 mg every 14 or 21 days	Intermediate action; faster release, which may cause mood swings.
Testosterone Association (Decanoate, etc.) (250 mg/mL)	Intramuscular (IM)	250 mg every 14 to 28 days	Less recommended; tends to cause intense hormonal peaks and mood swings.
Testosterone Gel (1% or 5%)	Topical	50 mg per day (1 sachet of 5g at 1%)	Promotes more stable hormonal levels with regular application; avoids injections.

Timeline of Effects (Transmasculine)

Effect	Onset	Maximum Effect
Increased Skin Oiliness/Acne	1 to 6 months	1 to 2 years
Facial/Body Hair Growth	3 to 6 months	3 to 5 years (peak)
Increased Muscle Mass/Strength	6 to 12 months	2 to 5 years
Body Fat Redistribution	3 to 6 months	2 to 5 years
Cessation of Menstruation	2 to 6 months	Considered Non-Applicable (presence/absence)

Effect	Onset	Maximum Effect
Clitoral Hypertrophy (Genital Virilization)	3 to 6 months	1 to 2 years (peak)
Voice Deepening	3 to 12 months	1 to 2 years (stabilization, definitive)
Androgenic Alopecia	After 12 months	Variable
Increased Energy (Physical/Mental)	1 to 2 months	Time until maximum effect is indefinite

Mental Health and Legal Framework

Mental Health is another fundamental pillar in trans health care. Studies indicate that the high rates of psychological distress observed in this population do not result from gender identity itself but from the effects of structural transphobia, social exclusion, violence, and stigma [7,18]. Therefore, psychological evaluation must be guided by a non-pathologizing perspective, focused on promoting autonomy, strengthening support networks, and mitigating the damage resulting from social oppression. It is a consensus in current guidelines that the presence of psychological distress, by itself, does not constitute a contraindication for access to hormone therapy or gender-affirming procedures [12,18].

The Brazilian legislation, through Resolution No. 2.427/2025 of the Federal Council of Medicine (CFM), updated the guidelines for the care of people with gender incongruence, establishing a minimum age of 18 years for the start of cross-sex hormone therapy and 21 years for surgeries with sterilizing potential, in addition to defining that monitoring must be carried out by trained multiprofessional teams [19]. The regulation also reinforces that health screenings must be performed according to the anatomical organs present, regardless of gender identity, ensuring the early detection of conditions such as breast cancer, cervical cancer, prostate cancer, among others [12,19].

International guidelines, especially the WPATH Standards of Care, Version 8, adopt a care model based on informed consent, eliminating the mandatory requirement for psychiatric reports to initiate hormone therapy or gender-affirming surgeries. This model reinforces the centrality of the trans person's autonomy in the care process, recognizing their capacity for self-determination [12].

Conclusion

Comprehensive care for transgender people is not limited to hormone therapy or surgical procedures but must include health promotion, prevention, rehabilitation, and surveillance actions, such as access to HIV pre- and post-exposure prophylaxis (PrEP and PEP), adapted oncological screenings, gynecological and urological care sensitive to gender specificities, guidance on fertility preservation, and monitoring of chronic clinical conditions [12,19].

Given all the above, it is concluded that clinical care for transgender people must be based on practices rooted in ethics, human rights, and the best available scientific evidence. Overcoming cisnormative practices and adopting care models centered on autonomy, welcoming, and comprehensiveness are essential to ensure that the right to health of this population is effectively realized, employing multiple therapies and cross-sex hormone therapy to ensure the gender affirmation of these individuals.

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Review Article

Surgical Sutures

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ABSTRACT

This study presents a review of the literature on different types of surgical sutures, highlighting their importance in medical practice for tissue synthesis. It reviews various suture thread types, categorizing them as absorbable and non-absorbable, in addition to differentiating them by origin (organic, synthetic) and structure (monofilament, multifilament). Their properties, such as tensile strength, biocompatibility, and tissue reactivity, are discussed, as well as the impacts of thread choice on wound healing. The study also mentions technological advances in manufacturing and criteria for appropriate selection based on scientific evidence.

Keywords: Surgical sutures; suture; wound healing; wounds.

Surgical suture threads play an essential role in medical practice, allowing tissue approximation and promoting wound healing. Historically, diverse materials have been used, including vegetable fibers, animal intestines, and metals, reflecting the constant technological evolution in the surgical field [(1).] With advances in material science, synthetic absorbable and non-absorbable threads have become widely employed, each with specific properties that influence their selection according to the type of tissue and the procedure performed [(2).]

The selection of the suture material depends on several factors, such as biocompatibility, mechanical strength, and capacity for degradation in the body. Studies have shown that the degradation of absorbable threads is directly related to the histological and physiological environment in which they are implanted. Factors such as pH, presence of

enzymes, and bacterial contamination can accelerate or slow the healing process, compromising the material's integrity and influencing the timeline [3]. For instance, polydioxanone (PDS) has been identified as one of the materials most resistant to degradation, while threads like Monocryl (glycolide and epsilon-caprolactone copolymer) and Vicryl (polyglactin copolymer [30% glycolide and 70% L-lactide with calcium stearate]) exhibit shorter absorption times and higher susceptibility to enzymatic degradation [3].

The correct choice of thread impacts the prevention of post-operative complications. Inappropriate selection can lead to infections, suture dehiscence, and delayed wound healing. Therefore, the surgical team must consider factors such as tissue type, suture tension, and the presence of biological fluids that may compromise the material's stability [1].

This review article aims to analyze the different types of surgical suture threads, their properties, degradation mechanisms, and impact on wound healing, providing grounds for a more judicious choice based on scientific evidence.

GENERAL OBJECTIVE The objective of this study is to analyze the different types of suture threads, their properties, degradation mechanisms, and impact on wound healing, providing grounds for a judicious and scientifically-based choice, in order to optimize clinical outcomes and minimize postoperative complications.

METHODOLOGY This study consists of a literature review on surgical sutures, analyzing their characteristics, classifications, and impact on tissue healing. To this end, scientific sources were consulted, including academic articles, books, and publications in databases such as PubMed, Medline, and Scielo.The inclusion criteria covered studies published in the last 20 years that discuss the different types of suture threads, their composition, biocompatibility, tissue reactions, and surgical applications. Priority was given to articles presenting comparative analyses and clinical trials on material effectiveness.The search was performed using descriptors such as "surgical sutures," "absorbable suture," "non-absorbable suture," "suture biocompatibility," and "wound

healing," ensuring a comprehensive and up-to-date approach. The collected data were organized into categories, considering the classification of the threads, their physical and chemical properties, as well as their effects on post-surgical recovery. Based on this information, a critical analysis was performed to identify the advantages and disadvantages of each thread type and guide the best clinical choice.

DEVELOPMENT Classification of Suture Threads: according to their degradation (absorbable or non-absorbable), their origin (organic, synthetic, mixed, or mineral), and the number of filaments (monofilament or multifilament) [2].

Characteristics of an Ideal Thread:

- High tensile and torsional strength;
- Regular and thin caliber;
- Low fluid retention (low capillarity);
- Good flexibility and low memory (resistance to unwinding);
- Low or no tissue reaction;
- Easy sterilization;
- Accessible cost [2].

Organic Absorbable Sutures Plain Catgut loses half its strength between 5 and 7 days and all strength within 3 to 4 weeks. It is a thread of biological origin, composed essentially of collagen obtained from bovine serosa. It is widely used for its absorption capacity (between 56 and 120 days) and easy handling [4].

Historically, its use dates back to Antiquity, having been employed by physicians like Galen and Avicenna. Joseph Lister improved its sterilization in the 19th century [5]. Chromic Catgut, treated with chromium salts, offers greater resistance (losing half its strength between 19 and 20 days) and lower tissue reactivity than plain catgut, besides delaying its absorption (from 56 to 120 days) [4]. However, it has limitations such as high tissue

reactivity, reduced knot security, and variation in absorption time [4,6]. Despite this, studies show that chromic catgut completely dissolves in 2.5% sodium hypochlorite solutions, demonstrating utility in dental simulations [6].

Synthetic Absorbable Sutures were developed to overcome the limitations of natural threads. They present lower inflammatory reaction, consistent mechanical strength until complete absorption, and different absorption times [2,7].

Monofilaments:

- Monocryl®: Good initial strength, easy handling, and low tissue reaction, absorbed by hydrolysis in 90 days.
- PDS® (Polydioxanone): Starts absorption after 90 days and completes in 180 days, with high strength (2,7).
- Maxon®: High strength and slow absorption, associated with a lower rate of abdominal infection compared to polyglycolic acid (2).

Multifilaments:

- Vicryl®: 90% glycolic acid and 10% lactic acid; 50% absorbed in 28 days and 100% after 70 days (2).
- Dexon®: 100% absorbed in 60 days. Associated with 16% infection in abdominal wall closure, according to studies (2).

Organic Non-Absorbable Sutures include silk, cotton, and linen, known for their strength and low cost. However, the multifilament structure favors bacterial retention and induces an intense inflammatory reaction (7,8). Silk, in particular, may inhibit macrophage function, stimulating greater TNF-alpha production, which worsens the tissue reaction and increases the risk of infections [8].

Synthetic Non-Absorbable Sutures are widely used in procedures requiring prolonged support, such as cardiovascular and orthopedic surgeries, and hernia repair [9,10].

Among the most used are:

- Nylon: Monofilament, with low inflammatory reaction and lower risk of infection. Provides excellent wound epithelialization [10,11].
- Polyester: High strength and stability.
- Polypropylene: High strength, low reactivity, and lower microbial colonization. Demonstrates better wound healing and lower infection risk compared to natural and multifilament sutures [10-12].

Nylon sutures are also considered safe for closing mucosa, skin, and muscles with a low complication rate [11]. Tensile strength is increased when associated with appropriate knotting techniques, such as the surgeon's knot [12].

Conclusion

The tensile strength of the suture site, the type of tissue being sutured, the thread absorption time, as well as the body's reaction to the thread, must always be taken into consideration.

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Essay

Neurobiological and Evolutionary Bases of Human Behavior: The Birth of Morality and Ethics.

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The first time I encountered Penny Spikins' work, my reaction was the most primitive possible: WOW! Simple as that. I could embellish and use academic jargon, but the fact is that her work, besides being innovative—even subversive—aligned with the research I develop. Obviously, nothing that comes close to the researcher's work, but it served to give me encouragement in continuing the research. Penny Spikins is a prominent researcher at the University of York who has dedicated herself to redefining the understanding of the origins of human connection, with a particular focus on pro-social motivations and the roles of vulnerability and care throughout human history [1]. Her book, "Hidden Depths: The Origins of Human Connection [2] and also "How Compassion Made Us Human"[4], represent a significant departure from traditional paradigms of human evolution. Spikins' work highlights a perspective that values emotions and social interdependence as fundamental pillars of evolutionary success, in contrast to the exclusive emphasis on intellect or individual competition that academia has always championed. She further posits that emotions, in contrast to the exclusive emphasis on intellect, constituted the essential driving force of the human evolutionary trajectory, inserting our history within processes that echo changes observed in other complex social mammals [2]. This approach challenges the linear and exceptionalist view of human evolution, which often portrays our species as an inevitable progression toward a "more perfect" form[2] . Instead, Spikins argues that human evolution was shaped by multiple paths, each with its own strengths, weaknesses, and adaptive compromises[2] . She also addresses the field of neurodiversity, with a marked interest in autism, investigating how cognitive diversity and multiple evolutionary paths intertwine in the formation of human sociality [1] . She rethought how human evolution occurred, and this aligned with my research and my definition of the concept of proto-morality. What she calls proto-socialization encompasses a great deal of the concepts of proto-morality, which is

nothing less than a proto-socialization. Her innovative work encouraged me to pursue the conceptualization of the structural bases that were formed during our evolution and that shaped our behaviors and life in society—that is, everything that we are.

Instinct, Proto-Moral, Moral, and Ethics

The first complex living beings exhibited a behavior of surviving at all costs and perpetuating the species. This was supported by a more rudimentary nervous system composed mainly of a brainstem, a rudimentary limbic system, and the pallium, which would be the basis of a future mammalian neocortex. These beings did not live in groups and had no parental care. What guided them was pure Instinct. Instinct is related to survival, mating, predation, and flight. Once initiated, it cannot be stopped. Today we can see this behavior in most reptiles.

With the emergence of mammals, particularly during the extinction of the large predators, there was a great shift in survival and feeding dynamics that favored the onset of cooperation as a strategy for species survival and perpetuation. This required learning new skills to cooperate in a group. This occurred through neurotransmitters and hormones, the development of new structures in the nervous system, and the integration of neural circuits. I begin to cooperate as a strategy to survive and perpetuate the species. A more elaborate limbic system starts to develop, and an incipient neocortex appears. This is Proto-Morality: I begin to cooperate, but I do not yet possess a neocortex capable of inhibiting instincts when present. Cooperation is always overridden by instincts. This behavior persists until the emergence of the first hominins when, with a more developed neocortex, I gain the capacity to inhibit instincts for the sake of group cooperation. This only occurs in the *Homo* genus—Morality.

Advancing a few hundred thousand years, when large sedentary settlements, such as in Sumer, emerge, with survival secured and cooperation skills consolidated, I begin to be able to reflect on questions that go beyond group norms. I begin to reflect on actions independent of time and space—Ethics.

The Relevance of the Neurobiological and Evolutionary Approach in the Study of Human Behavior

The study of contemporary human behavior requires a transdisciplinary academic synthesis, as it draws from different sources such as psychology, medicine, philosophy, sociology, archeology, and many others.

Current human behavioral patterns are the result of adaptations forged in ancestral environments to optimize survival and reproduction, which necessarily involved group cooperation[6]. And this behavior occurs through an intricate architecture and a complex,

dynamic interaction between genetic, environmental, and neurobiological factors[8]. The structure of the brain, composed of billions of neurons and their synapses, is the basis for learning and knowledge, with neuroplasticity allowing the continuous reorganization of the brain in response to new information and experiences[9]. The co-evolution between cerebral capacities and social behavior is a central axis of this understanding, with intelligence being conceived not only as an individual attribute but as an adaptation to a lifestyle characterized by social interdependence and the utilization and transmission of knowledge[11]. This integrated approach is crucial for a complete understanding of the complexity of human behavior.

Emotions as the Driving Force of Human Evolution

Spikins emphasizes that emotional intelligence, compassion, and the ability to form deep bonds, and not just cognitive intelligence, were intrinsically linked to the evolutionary success of our species[2]. The ability to genuinely care for the well-being of others, extending to family members and even strangers, is presented as a quintessential human trait, fundamental to the formation of complex societies[5]. Compassion, in particular, is placed at the heart of human identity, being an element that unites and inspires us[14]. This re-evaluation of what constitutes "success" in an evolutionary context suggests that characteristics often perceived as "weaknesses" in modern competitive societies, such as emotional sensitivity or vulnerability, may have been crucial adaptive advantages in our deep past, shifting the focus from individual metrics to group resilience and social cohesion.

Spikins outlines three crucial transitions in the human trajectory where the development of emotional capacities proved decisive[2]:

Two Million Years: The incursion of human ancestors into new ecological niches drove the emergence of new forms of collaboration. This included the development of care systems for vulnerable group members, such as the sick or injured. These emotional adaptations were not isolated; they catalyzed cognitive changes, as new connections based on compassion, generosity, trust, and inclusion reconfigured human relationships, including those with material objects[2]. This period marks the beginning of deeper social interdependence, where mutual care became a pillar for group survival and flourishing.

300,000 Years: A subsequent transition in human emotional capacities occurred, characterized by an increase in social tolerance. This allowed the ancestors of our own species to extend their network of care and alliance beyond the immediate local group, reaching distant allies. This expansion of the social network gave human communities enhanced resilience in the face of environmental changes[2]. In parallel, the emergence of an increasingly intimate relationship with animals and possessions was observed, a phenomenon that Spikins interprets as a response to new vulnerabilities and the search

for comfort and belonging in a complex world[2] This ability to form emotional bonds beyond the immediate circle of kinship and even with the non-human world is a testament to the depth and breadth of human emotional sensitivities.

Neanderthals: Spikins dedicates a part of her analysis to our close cousins, the Neanderthals. She reveals them as beings equally capable of care, but with distinct emotional dispositions. Instead of viewing them as an inferior form, Spikins presents them as humans who followed a different evolutionary path, with their own strengths, weaknesses, and adaptive compromises[2]. This perspective challenges the notion of a linear and inevitable progression toward *Homo sapiens* as the "perfect form"[2]. Vulnerability and the willingness to care for others, while crucial for evolutionary success, are concepts that, for modern cultures, may be strangely disturbing, given the emphasis on selfish competition[13]. Spikins' analysis suggests that the diversity of evolutionary paths is a fundamental characteristic of hominin history, and that success is manifested not in a single ideal form, but in a variety of social and emotional adaptations.

Vulnerability as an Adaptive Advantage

In a conceptual twist, Spikins proposes that vulnerability, far from being a weakness to be overcome, was a fundamental catalyst for human evolutionary success. The conventional understanding of natural selection often emphasizes strength, independence, and the ability to overcome adversity as the main drivers of survival. Spikins' work presents an alternative perspective: the physical and emotional vulnerability of our ancestors generated an intrinsic need for mutual care and support.

This need for care, in turn, fostered the development of deep emotional commitments between individuals. These commitments were not merely passive feelings but rather the foundation for deep collaboration, where group members actively supported each other in the presence of illness, injury, predator risks, or hunting dangers[15]. This intensified collaboration was the starting point for significant changes in the human trajectory, including the notable expansion of the neocortex that characterizes us as a species[13]. The underlying logic is that a larger and more complex brain, while offering cognitive advantages, also required a prolonged period of development and dependence, making individuals more vulnerable for longer. Collective care made this vulnerability manageable, allowing the benefits of brain development to manifest.

The archaeological evidence of care and assistance is found in periods of human evolutionary history more remote than the evidence of interpersonal violence, which is significantly more emphasized by the traditional canon[13]. This observation suggests that the capacity for care and social interdependence were not mere late additions, but rather intrinsic and early characteristics of the human lineage. Emotional interdependence, manifested through compassionate responses and mutual emotional commitments, is

presented as a central pillar of human evolutionary success, allowing groups to thrive in challenging environments[13]. Instead of a purely selfish evolution, Spikins demonstrates that the ability to form bonds and offer support was a decisive factor for the species' resilience and adaptability. This reframing of evolutionary success challenges the modern perception that success lies solely in individual competition, suggesting that the capacity for care and connection was as, or more, important than physical strength or brute intelligence for human survival and development.

The Formation of Deep Emotional Connections

The human capacity to form deep emotional connections was not restricted to interactions between individuals of the same species. According to Spikins, this emotional sensitivity extended beyond human bonds, encompassing a growing and significant relationship with animals and even with inanimate objects, which became "valued possessions"[2]. This expansion of the scope of emotional attachment is interpreted as an adaptive response to new human vulnerabilities and an intrinsic search for comfort and a sense of belonging in a constantly changing and, at times, challenging environment[2.]

This extension of emotional connections reflects a profound psychological need for security and solace. In an uncertain and dangerous world, the ability to find comfort in pets or symbolic objects may have provided emotional stability, contributing to individual and group resilience. The relationship with animals, for example, may have evolved from a purely utilitarian interaction (hunting, protection) to one of companionship and attachment, as evidenced by the burial of dogs, suggesting a fluidity in attachment that extends beyond the species itself[3]. Likewise, the valuing of objects, which transcends their practical function, may have provided a sense of continuity and identity, acting as "objects of attachment" that mitigated loneliness or anxiety, reinforcing the sense of belonging to the group[3]. These behaviors demonstrate the flexibility and depth of human emotional capacities, which adapted to find support and meaning in various forms of connection.

Neural Circuits of Empathy and Compassion

The neurobiological basis of empathy and pro-social behavior is a complex and interconnected system, involving a network of CNS connections and modulation by various hormones and neurotransmitters[17]. Empathy is conceptually divided into two main components: affective empathy, which refers to the capacity to share the emotional experiences of others, and cognitive empathy, which involves the ability to understand others' perspectives and mental states[17]

Affective Empathy: This component of empathy is intrinsically linked to brain regions such as the anterior insula and the anterior cingulate cortex. Functional neuroimaging studies show that these areas are consistently activated when individuals observe others in suffering or pain, reflecting a neural resonance and a sharing of emotional experiences[17]. The amygdala, a brain structure traditionally associated with emotional processing and threat detection, also plays a crucial role in empathy, especially in recognizing and responding to emotional expressions of fear and distress, which can motivate pro-social behavior[17]. The activation of these regions underscores the biological basis for the human capacity to "feel with" others, a prerequisite for compassion and care.

Cognitive Empathy: This aspect of empathy depends on the neural network, which includes the medial prefrontal cortex, the temporoparietal junction, and the posterior superior temporal sulcus[17]. These regions are essential for understanding the beliefs, intentions, and perspectives of other people, allowing for a "reading" of the other's mind. The ability to adopt the perspective of the other is fundamental for complex social coordination and moral decision-making, allowing individuals to anticipate others' needs and reactions.

Mirror Neurons: One of the most notable findings in social neuroscience is mirror neurons. This network of brain cells exhibits a unique characteristic: they fire both when an individual performs an action and when they observe the same action being performed by others[19]. The mirror neuron network is believed to be fundamental for imitation, understanding the actions and emotions of others, and the development of empathy and social connections, allowing for an internal "simulation" of the other's experience[19]. This ability to "mirror" others' behavior and emotions provides a neurobiological basis for emotional resonance and "emotional contagion," where emotions are transmitted between individuals[22]. The activation of these neural networks underscores the depth of the biological bases for emotional capacities as drivers of human evolution.

The Role of Neurotransmitters and Hormones in Social Modulation

The modulation of social behavior and cognition is intrinsically influenced by a complex interplay of neurotransmitters and hormones, which act on various neural pathways.

Oxytocin and Vasopressin: These neuropeptides are recognized for their crucial role in modulating complex social behaviors and social cognition[27]. Oxytocin, in particular, is widely studied for its association with the formation of social bonds and attachment. Its action includes increasing dopamine release in the nucleus accumbens, a brain region vital for reward processing, which, in turn, induces feelings of pleasure and attachment, essential for forming social bonds[29]. Studies show that its administration can amplify empathetic responses and increase the propensity for pro-social behaviors[17]. Genetic variations in the genes coding for Oxytocin and Vasopressin receptors can explain part of

the individual diversity in human social behavior[27]. Their influence is complex and can be modulated by individual and contextual variables, potentially influencing preference for ingroup members[31].

Dopamine: This neurotransmitter is strongly associated with the brain's reward system, playing a central role in motivation and the experience of pleasure[8]. Participation in pro-social acts activates reward pathways in the brain, leading to the release of dopamine and the generation of positive feelings, which serves as a reinforcement mechanism, encouraging the repetition of such behaviors[17.] Dopamine is also involved in mood regulation and cognitive functions, and when dysregulated, it may be linked to Parkinson's disease and schizophrenia[32].

Cortisol: Cortisol and the hypothalamic-pituitary-adrenal (HPA) axis, the body's main stress response system, are intrinsically connected to empathy[33]. Empathetic processes can be compromised or interrupted in the absence of adequate activation of this axis, indicating a link between stress regulation and the capacity for empathy[33]. This suggests that the ability to respond to stress and to emotionally connect with others are interconnected processes in the brain.

Neuroplasticity and Social Learning

The human brain is remarkably characterized by its neuroplasticity, an intrinsic capacity to reorganize, form new neural connections, and modify synapses in response to experiences and the environment[9]. This is fundamental for learning and memory processes, allowing the brain to continually adapt to new information, skills, and social contexts, making learning a continuous and dynamic process[10] and was particularly accentuated and prolonged during human development. This characteristic confers enhanced cognitive flexibility and facilitates the acquisition of complex social and technical skills, which are crucial for adaptation and success in diverse environments[10].

The anatomy and function of the human brain evolved to be highly responsive to environmental experience, especially through social interactions[34.] This means that the social environment not only influences individual development but can also have transgenerational biological effects.

The social environment, including the quality of maternal care, socioeconomic status, and exposure to stressors, can induce epigenetic modifications. Epigenetics studies changes in gene expression that occur without altering the DNA sequence, but which can influence behavior, cognition, and mental health[36]. It basically consists of the activation or suppression of genes through acetylation or methylation in response to the environment. Early childhood experiences, such as maternal care and socioeconomic status, can shape the structure and function of the brain, influencing behavior and mental health outcomes[8].

Furthermore, psychosocial stressors, such as maternal stress during pregnancy or childhood trauma, can lead to epigenetic changes that affect gene expression and brain development, with implications that can be transmitted across generations[37]. This reveals a deep causal cycle: the social environment (e.g., quality of care, stress) can lead to epigenetic changes, which in turn alter gene expression and brain development, resulting in different behavioral outcomes (e.g., anxiety, prosociality). This process suggests that the social conditions experienced by one generation can literally "mark" the biology of future generations, deepening Spikins' argument about the critical role of social connections and care, extending it to a biological inheritance of social experience that can make entire populations more or less predisposed to certain behaviors or vulnerabilities. This phenomenon suggests that the experiences lived by one generation can leave biological "marks" that influence the biology and behavior of subsequent generations, adding a layer of complexity to the understanding of inheritance and adaptability. For example, in mice, maternal diet can influence DNA methylation patterns in the offspring, affecting characteristics such as fur color and predisposition to obesity, and these changes can be transmitted to the pups[64]. Although the transgenerational inheritance of epigenetic marks induced by psychosocial stressors is a controversial aspect, the possibility that an individual's responses to social and behavioral stressors can be transmitted to future generations is an expanding research field[37]. This means that the social environment can have a cumulative and long-term impact on human neurobiology and behavior, far beyond what is typically considered "genetic," adding a profound dimension to the understanding of interdependence and care.

The relationship between brain development and social complexity is a classic example of co-evolution. Initial cooperation within human groups not only facilitated survival but also exerted a selective pressure for cognitive enhancement. In turn, this cognitive enhancement allowed for more sophisticated forms of cooperation, creating a positive feedback loop that stabilized and deepened social relationships[11] This co-evolution process suggests that cooperation and cognition reinforced each other throughout human history[11].

The "social brain" hypothesis posits that sociality is at the heart of cognitive evolution. The increase in brain size, the reorganization of its structures, and notable neural plasticity are seen as adaptations that allowed humans to maintain larger and more complex social networks, as well as form more intimate and lasting social relationships[11]. This plasticity, in particular, facilitated social learning and cultural transmission, key elements for the species' adaptability[34]. The functional flexibility of our neural structure allows for the acquisition of cognitive capacities not directly selected by evolution, such as language in different modalities and cultural skills like mathematics and programming[34].

Archaeological Evidence of Care and Social Interdependence

Archeology, through meticulous discoveries, provides concrete and tangible evidence of care practices and social interdependence dating back to ancient hominins. These discoveries directly challenge the once-common perception of our ancestors as "tough and insensitive" beings, devoid of emotional complexity[13]. The evidence of care and assistance is found in periods of human evolutionary history more remote than the more widespread evidence of interpersonal violence[13].

Homo erectus (Dmanisi, Georgia, ~1.77 million years ago): In the Dmanisi archaeological site, the remains of an elderly *Homo erectus* individual were found who, at the time of death, had lost almost all his teeth. Analysis of these remains strongly suggests that the group to which this individual belonged actively assisted him with food processing and consumption, as he would not have been able to chew on his own[65]. This finding is one of the oldest pieces of evidence of altruistic behavior and care for the elderly, indicating that such practices may have developed very early in the hominin lineage, possibly at least two million years ago[66]. The survival of this toothless individual for a prolonged period before death points to continuous assistance and dependence on the group for basic subsistence activities[66].

Homo heidelbergensis (Sima de los Huesos, Atapuerca, Spain, ~430,000 years ago): The skull of a young female, nicknamed "Benjamina," an *Homo heidelbergensis*, revealed a condition of craniosynostosis (premature fusion of cranial sutures)[67]. Despite this congenital deformity, which would have caused serious neurological and motor problems, "Benjamina" survived for approximately a decade (10–12 years)69. Her survival would have required continuous assistance with feeding, protection, and possibly mobility, provided by her group. This case is interpreted as robust evidence of community care and social empathy in an ancestral species, suggesting that care emerged deep within the *Homo* genus, and not as a late characteristic of our own species[69].

Neanderthals (~450,000–40,000 BC): Neanderthal populations, often simplistically portrayed as brutal, exhibit notable progress in terms of compassion. Archaeological evidence indicates that family and social groups cared for vulnerable members for long periods, often throughout their lives, even those with severe injuries that prevented them from walking or affected their cognitive abilities[15]. This suggests the existence of strong pro-social bonds and the generalized practice of medical treatment and assistance, demystifying the image of a purely individualistic species[72]. The capacity for care and social interdependence were not mere late additions, but rather intrinsic and early characteristics of the human lineage. The early appearance and persistence of care for the disabled and vulnerable suggest that these behaviors were deeply rooted and

adaptively beneficial, reinforcing the idea that interdependence, rather than radical independence, was a distinctive characteristic of human success.

Conclusions

The neurobiological and evolutionary bases of human behavior reveal a rich and multifaceted narrative that challenges and expands traditional understandings of evolution. Emotions, vulnerability, and the capacity for care were central driving forces in the human trajectory, rather than mere byproducts of intellect or competition. This perspective redefines evolutionary success, shifting the focus from individual fitness to group resilience and social cohesion, where interdependence becomes a fundamental pillar.

Contemporary neurobiology corroborates this view, demonstrating that empathy and prosociality are rooted in complex neural circuits, modulated by neurotransmitters like oxytocin and dopamine, and influenced by notable neuroplasticity. The human brain's capacity to adapt and learn socially, along with the influence of epigenetics—which allows the inheritance of environmental experiences across generations—underscores the profound interconnection between biology, environment, and social behavior. This means that the social and emotional conditions experienced by one generation can literally shape the biology of future generations, emphasizing the cumulative impact of the social environment on human neurobiology.

Evolutionary theories of altruism and cooperation, which extend beyond kin selection and direct reciprocity, provide new elements for understanding social behaviors. The co-evolution between the brain and sociality, exemplified by the "cognitive niche" hypothesis, highlights how cognitive enhancement and social complexity mutually propelled each other.

The archaeological evidence provides powerful empirical validation for the new theories about human behavior. Discoveries at sites like Dmanisi and Sima de los Huesos, as well as the study of Neanderthal remains, reveal a consistent record of caring for vulnerable individuals over millions of years of hominin evolution. These findings demonstrate that interdependence and compassion were not late or marginal characteristics, but rather deeply rooted and adaptively beneficial behaviors, essential for the survival and flourishing of our ancestors.

These new elements, and in particular Spikins' work, provide a transformative view of human evolution. These new perspectives have profound implications for understanding human nature, social values, and future research priorities, suggesting that a society that values interdependence, care, and diversity may be more aligned with the deep foundations of our own evolutionary history.

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