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EDITORIAL

# Academic integrity

*Irene Durante-Montiel*[1], *Ángel Morales-González*[2], *and José A. Morales-González*[3]*

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Academic integrity finds its purpose in the three essential objectives of higher education institutions. These are: first, the training of human resources with a high educational level and social commitment; second, the generation of new knowledge through research *verbi gratia*, technology transfer, its publication, and application in society; and finally, outreach, extension, and dissemination of university activities: conferences, courses, continuing education, congresses, etc.

This work focuses on academic integrity related to the essential objective of generating new knowledge and therefore addresses the publication of articles and their retraction. That is, the withdrawal of a published article constitutes the clearest evidence of a failure in the scientific method and/or in the academic integrity of the author(s).

First, human behavior is driven by free will and is perceived in the following ways:

- Giovanni Pico della Mirandola, an Italian humanist and thinker who lived in the 15th century, published in Rome in 1486 his Conclusiones philosophicae, cabalisticae et theologicae, known as "The 900 Theses." These are nine hundred propositions collected from diverse cultural sources, with great influence in his time, including Latin and Arab philosophers and theologians. In these propositions, we find an imaginary dialogue: "Abdala el Saracen, asked what he considered the most wonderful spectacle in this world, replied that he saw nothing more splendid than man." "I have placed you at the center of the world so that you may more conveniently observe all that exists in it."
- In the philosophical realm, Jean-Paul Sartre, establishes: "Neither God has given us an irremediable destiny, nor do nature or society absolutely determine our possibilities, our conduct. We are what we have wanted to be and we can always cease to be what we are."
- For a scientist, science is above all a way to discover the truth about the phenomena of the universe, and it does so through scientific research based on the scientific method as the primary tool to achieve its goal. However, science can be falsified and distorted by an unethical researcher. An unethical researcher puts personal interests above the intrinsic ethical values that every professional and academic is supposed to have. Science itself generates ethical and social links, such as honesty and the need for cooperation and social exchange.

From the above, we can conclude that our actions are driven by conscience, freedom, and will; there are no good or bad things, only consequences.

In the past 25 years, the publication of all types of documents (original articles, reviews, book chapters, books, etc.) has increased, favored by the use of the internet and open access to information. This is a faster process, but not necessarily simple. On the other hand, there are various circumstances that lead some researchers to make unethical decisions regarding article publication, such as legislative gaps, economic reward (scholarship systems), obtaining a job position, prestige and recognition, or institutional pressure. They do this through plagiarism, authorship problems, duplication of information, methodological flaws, ethical issues, fabrication of results, and editorial process failures, among

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others. Using scientific search engines, such as PubMed, Scopus, or Web of Science, documents (articles, books, etc.) that have been withdrawn after publication can be identified, which undoubtedly shows the lack of academic integrity of the authors. A particular situation is that some journals, when withdrawing a published article, mention it as an *erratum*, which can cause confusion because recognizing an error is very different from withdrawing an article due to a lack of academic integrity. In our country, there are about 30 documents classified as retractions and erratum.

A very important point is the consequences that occur when this type of behavior by some researchers is discovered. First, if we look in the science law, the term plagiarism does not appear, nor in scholarship systems; only ethical responsibility or unethical conduct can be observed. University regulations or statutes that govern the behavior of their academics (professors-researchers), due to their age, also do not contemplate such conduct as information plagiarism, creating a legal gap for this type of behavior. Therefore, it is important to monitor the protocols or projects developed in research units by different committees. These include the Research Ethics Committee, Research Committee, Bioethics Committee, and the Internal Committee for the Care and Use of Laboratory Animals.

We believe that the best measure to prevent such conduct, such as a lack of academic integrity, is prevention. This focuses on education at various educational levels, high school, undergraduate, and graduate (undergraduate, graduate, and post-graduate) for the proper training of students in subjects or learning units on research methodology, ethics, bioethics, morality, deontology, and others. For this, it is necessary to include healthy lifestyles and doing things well.

*"La gracia es gratuita, es un don; aquel que lo recibe, el agraciado, si no es un malnacido, lo agradece: da las gracias"*

– Octavio Paz

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ORIGINAL ARTICLE

# Workload in general dentistry, its ergonomic implications and remedial perspectives

*Abhinav Sharma[1]*, J. Ramkumar[1], Shalini Gupta[2], and Ayushi Jain[2]*

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## Abstract

*Dentistry is a physically demanding profession that requires clinicians to manage a wide range of oral health conditions, from routine caries to more complex pathologies. Advancements in dental materials and treatment techniques have improved patient outcomes, but the core clinical procedures remain largely manual and repetitive. Combined with an imbalanced patient-to-dentist ratio, these factors place significant physical demands on practitioners, who frequently adopt awkward postures for extended periods. As a result, many dentists face a heightened risk of work-related musculoskeletal disorders (WMSDs), which can compromise their health and career longevity. This work is a combination of a literature review augmented with a field survey to examine the ergonomic issues inherent in general dental practice and highlights how conventional preventive strategies often fall short. To support this analysis, we conducted a structured survey among practicing dentists to map common risk factors. Based on these insights, we propose a conceptual collaborative robotic system that can share the physical workload and reduce postural strain. By combining literature review and risk assessment, this study emphasizes the need for integrated solutions that go beyond awareness campaigns or isolated design tweaks. The findings suggest that a thoughtful blend of ergonomics and robotics could significantly improve working conditions for dentists, lowering the prevalence of WMSDs and promoting sustainable professional wellbeing.*

***Keywords:*** *Dental ergonomics. Occupational health. Musculoskeletal disorders. Risk mitigation. Collaborative robotics. Clinical practice. Digital dentistry.*

## Introduction

The extent to which technological innovations have entered human lives is immense. In the last two decades, the methods and applications of such innovations have grown manifold. Industry 4.0, in recent times, has started reshaping the manufacturing and service sectors also. Dentistry has also evolved on similar lines and grown both in market size and usage of technology. However, increasing footfall in the dental clinics aspires for better technology to comprehend the ease of patients and, at the same time, keep a check on the health of the practicing clinicians.

It is essential to understand the impact of dental diseases and their economic and demographic perspectives. The World Health Organization (WHO) reported nearly half of the world population suffering from some form of oral disorder, with specific stress in the low- and medium-income countries (LMIC). In 2015, the global expenditure for dental treatments accounted for around 544 Bn USD, which is around 4.6% of the total medical expenditure. In a comparative analysis in the EU, dental treatment ranked third in terms of expenditure, with only diabetes and cardiovascular diseases above it. Consequently, the average global per capita expenditure on oral health is expected to grow steeply[1]. However, the WHO Global Oral Health Status Report 2022 claims oral diseases to be ranked as the number one global health issue.

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Oral disorders are rooted in multiple variables, including pathology, genetics, injuries, chronic comorbidities, dietary deficiencies, and lifestyle malpractice[2]. The resulting anomalies, hence, are unique in nature and need specific diagnosis and treatment. The evolution of technology and medicine has been on similar lines. Recent trends include the use of regenerative medicine, biomaterials, rapid prototyping for prosthetics, advanced Imaging, and surgical interventions[3]. While some of these have gained popularity, others, such as advanced robotics, artificial intelligence, augmented reality, and telemedicine, are still in their budding stages[4]. Understanding and treating oral carcinomas and designing novel implants have been fascinating and challenging enough for researchers and industries. Table 1 shows a list of the most common oral disorders[5-7].

General dentistry is more physically demanding, and the work nature is more quantitative rather than being subjective. Often, dentists have reported being underutilized in their skills. The treatment protocol is already established, and the dentists do not feel influenced by it, thereby creating cognitive load as well[6,7]. Dentists practicing in public health centers in Turkey eventually emphasized the need for increasing the staff members to map the imbalance of workload on existing staff[8]. In a contrasting comparison, the total oral health workforce (including dentists, hygienists, assistants, and technicians) is nearly 4 million, whereas the total affected population is around 3.5 billion. The average global density of dentists is 3.28 dentists/10,000 population, which is a serious challenge. This ratio even gets worse in specific areas of LMICs. In Taiwan, the same ratio was reported to be 5 dentists/10,000[9]. Hence, it is evident that dentists globally are affected by work overload, and it deters their cognitive skills and physical health[10].

Adding on to the challenges of workload, examining and treating the oral cavity is even physically tiring, owing to its convoluted biomechanics and tissue structures. The mandibular constraints do not allow for visible diagnosis, and thus, planning the treatment is always tedious, involving the use of mirrors[11]. The restricted space of the oral cavity keeps the instrumentation limited and results in loss of dexterity and demands a high level of accuracy for precise movements. This additionally affects the sitting balance. The use of the dental chair is at the center of some issues; although it is convenient for the patients, it is contrastingly ergonomically tiring for the dentists[12]. In the preliminary learning stage, dental students often find indirect viewing to be procedurally difficult and hence tend to adopt awkward and bad postures, which eventually lead to the development of work-related musculoskeletal disorders (WMSD)[13].

**Table 1.** Globally prevalent oral disorders

| No. | Disorder | Prevalence (% population) |
|---|---|---|
| 1. | Caries (permanent teeth) | 36 |
| 2. | Caries (deciduous teeth) | 8 |
| 3. | Severe periodontitis | 11 |
| 4. | Severe tooth loss | 3 |
| 5. | Oral cancers | 2 |

Over the last few decades, a lot of technological advancements have been introduced in Dentistry. The current trends and research are focused on painless treatment and patient comfort. However, the fundamental operative protocol in general dentistry has not changed much and still revolves around the use of a dental chair. The economic load of dental diseases has been almost constant temporally, and the workload on the clinicians has not improved. There exists a global deficit of trained dentists to treat oral diseases. The ever-increasing workload in general dentistry results in a physical and psychological impact on the overall health of practitioners. The situation worsens with the methods employed owing to the workspace constraints and mandibular restrictions, which cause muscle fatigue and eventually WMSDs.

In the following section, we shall discuss the persisting issues in the dental chair and postural requirements and explore the concerned ergonomic effects.

## Methodology

The primary research questions addressed in this work are *"Impact of workload and Postural Ergonomics on Dentists"* and *"Prospects of Collaborative Robots in addressing the Impacts."* To incorporate this, a two-tier mechanism was adopted. First, we did a comprehensive review of the literature, and subsequently, based on the insights, we performed a risk assessment survey with practicing clinicians to analyze the pitfalls in current practices and identify prospective preventive measures.

In the first part, the literature review was done through PubMed and Web of Science, web databases, which have an extensive repository. To incorporate all

relevant studies, the search keywords chosen were "(Postural Ergonomics) AND/OR(Ergonomics) AND (Musculoskeletal Disorders) AND (Muscle-Fatigue) AND (Digital Dentistry) AND (ROBOTIC DENTISTRY)". The search included review articles and research works published in English between 2005 and 2025. The search was refined to include only research/review articles, meta-analyses, and clinical trials. We selectively excluded editorials, letters, and only abstracts. A total of 454 (WOS) and 236 (PubMed) (690 in total) articles were produced. The duplications were removed using an Excel spreadsheet. This resulted in a total of 632 papers. Three papers were further excluded, which were classified as retracted. Finally, 629 papers were screened for eligibility using the PRISMA framework. The PRISMA flow diagram is shown below in figure. 1. The consolidated report revealed 62 papers that are included in framing this review.

In the second part, we conducted a subjective questionnaire-based survey in a public dental hospital in Lucknow, India. The participants were practicing dentists and final year students in their internship period. The questions were designed to assess the potential risks in dental offices and the severity associated with them. Subjective questions were asked based on their feeling, comfort, ease of operation, effect on muscle fatigue, and other cognitive aspects of design. This is discussed in subsequent sections. This two-layer methodology helped us in better understanding of the current practices in the clinics and recent topics of research for addressing the issues of concern.

## Dental chair, postural compromise, and musculoskeletal disorders in dentists

The standard protocols for examining and treating the oral cavity are designed around the dental chair. They require repetition, overhead work, extended stretching, and awkward bending. The human skeleton, however, is not suited for extended time in a fixed posture[14].

The quantum of research done in ergonomic improvements in dentistry revolves around the dental chairs. In most of the available ergonomic studies, the approach of researchers has been limited to modifying the dental chair. To incorporate user satisfaction and dentists' ease, multifunctional chairs have been developed and tested[15,16]. Most of such chairs include features such as an adjustable patient seat, a pressure water jet, an adjustable light, and desktop tools. These chairs are automatically controlled by hydraulic/pneumatic actuators or linear actuators in recent chairs[17-19]. However, these modifications are definitely able to achieve patient comfort, but do not tend to solve the issue of postural compromise of dentists. The major reason is the structurally disintegrated system design.

Postural discomfort in dentists arises from two major points: the constrained three-dimensional workspace around the dental chair and the ultimate need for indirect viewing of the oral cavity. The design of treating the patient on a dental chair inevitably requires an indirect view of the oral cavity at some point of time[20]. However, this itself becomes a cognitive load on the beginners, and they tend to bend in for a direct view of the oral cavity. With increased clinical experience, dentists attain better hand-eye control and cognitive maturity. To achieve the required skill, muscle activity and postures are compromised, which eventually tend to convert into chronic pain and WMSDs. To solve this, major developments have been made, such as the introduction of CAD/CAM systems for restorations, intra-oral scanners for imaging, and chair-side milling machines[21].

Another major challenge faced by dentists because of the dental chair system is that of dexterity. General dentistry is a precision-based science; in order to prevent injuries in the oral cavity, dexterity is of utmost importance. However, most of the dental chairs are designed for right-handed clinicians and may result in loss of motor dexterity in the early stages of the career itself[22]. A survey done on dentists concludes that around 97% of the left-handed clinicians are affected by the available workspace resources[23]. In fact, admission tests in many institutes pertain to dexterous skills as a prerequisite for dentists. Figure 2A shows a protocol-neutral posture expected from a dentist. Figure 2B represents a conceptual sketch of postural compromise a dentist experiences during normal procedures such as scaling and examination.

These modalities of operating on a dental chair in a constrained workspace and improper postures lead to WMSDs in dentists. Strikingly, around 68-100% of dentists suffer from WMSD in some part of the body. Most commonly affected parts are the neck, shoulder, and the lower back[24]. Some studies have highlighted the occurrence of MSDs associated with gender, and female clinicians being more affected[25,26]. The development of WMSD, however, is not a single event but a staged process. The muscular fatigue and imbalance caused by prolonged static postures lead to ischemic physiology that causes pain and muscle contraction. The contracted muscles create an asymmetrical stress on the skeleton, which eventually becomes MSD[27-29].

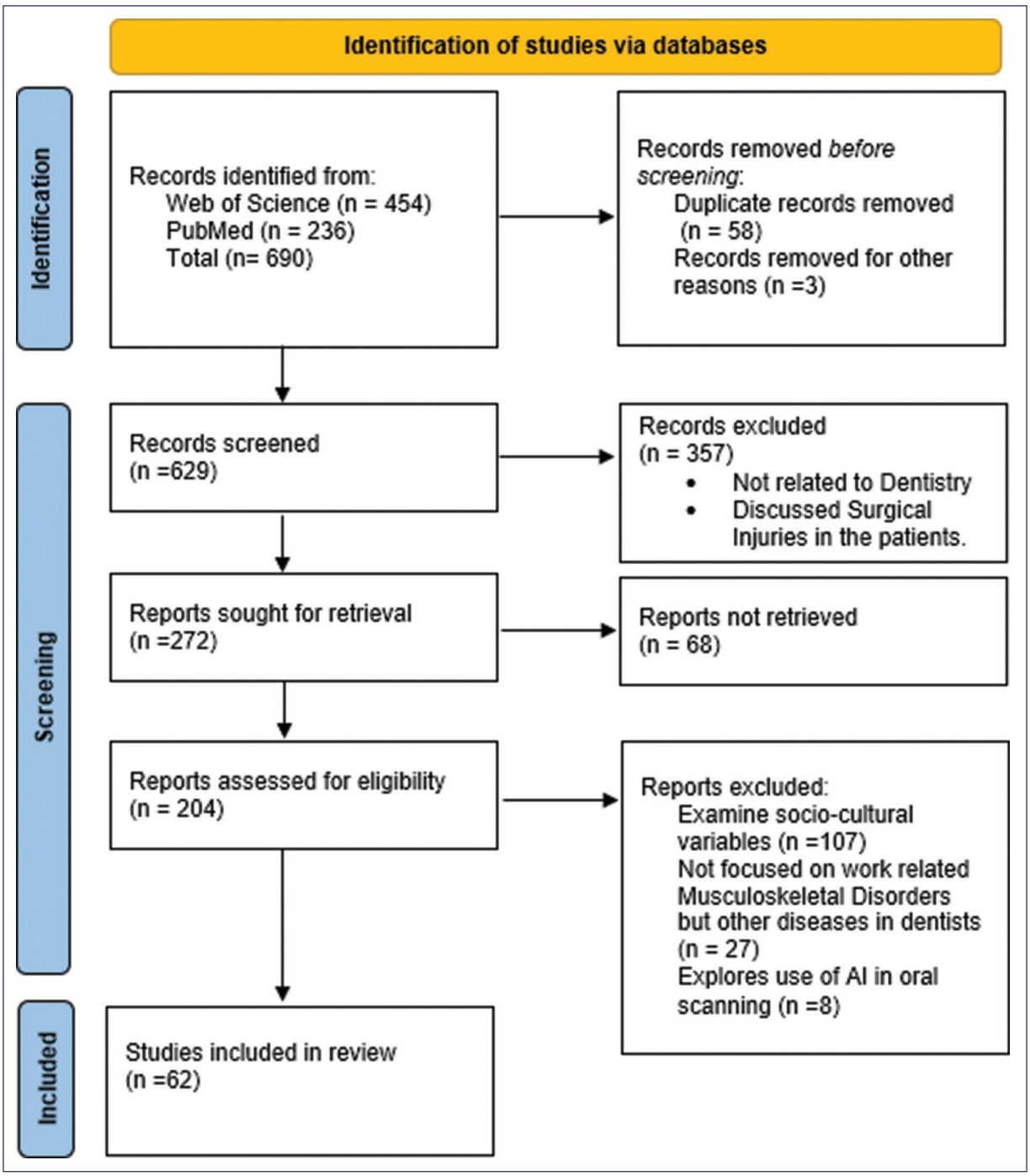


**Figure 1.** PRISMA flow diagram of the selection and exclusion criteria of the review.

The most common WMSDs prevalent in dentists are explained in table 2[30-33].

Prevalence of the WMSDs among dentists tends to reduce work efficiency and also cause economic losses, even leading to untimely retirements[29]. With such a wide range of critical aspects of WMSDs, there are very few available methods to overcome these problems. Most of the methods report judicious use of workspace, suggest taking sufficient work breaks, and maintain neutral work postures[30]. Sustainable practices that can help mitigate the ill-effects of WMSDs include maintaining the back curve to a minimum, using magnification instruments, switching sit-stand postures, maintaining grounded feet, regular stretching, and adopting physiotherapies[31,32].

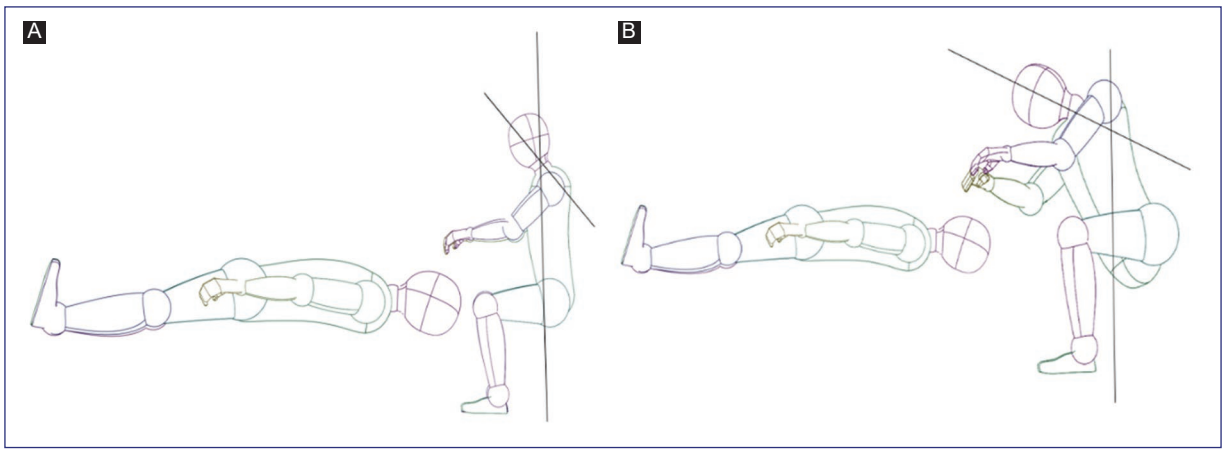


**Figure 2. A:** neutral posture to be maintained by dentists for physiological health. **B:** a dentist experiencing bending and twisting of the neck and a misaligned back.

**Table 2.** Common work-related musculoskeletal disorders in dentists, extent of affected, and reported population metrics

| No. | Musculoskeletal disorder | Affected body part | Motion anomalies | Affected population (%) |
|---|---|---|---|---|
| 1. | Carpal-tunnel syndrome | Wrist | Repetitive bending, vibrations, and hard gripping | 15-45 |
| 2. | Tendonitis | Neck | Prolonged bending during examination and procedures | 26-92 |
| 3. | Chronic pain | Lower back | Prolonged bending during root cleaning and gingival probing | 25-95 |
| 4. | Trapezius myalgia | Shoulder | Tool holding, lifting, loading | ~45 |
| 5. | deQuervains disease | Elbow | Tool holding, lifting, vigorous movements | 5-10 |

A number of studies and clinical trials conducted on practicing dentists and students reported that under strict ergonomic protocols, the trend of WMSDs shows a decline[33,34]. However, it is difficult for clinicians to practice these protocols owing to multiple factors such as excessive workload, practice habits, difficulties in using magnification tools, forgetfulness, and cognitive load of using multiple tools together[35].

Use of technology in dentistry is still being done standalone, and the entire practice is built around the use of a comfortable dental chair. However, its implications on ergonomic losses are not accounted for extensively. The need for magnifying instruments for an indirect view of the oral cavity and a limited three-dimensional workspace makes the development of a comprehensive technology for a one-point solution still far-fetched. The segregated use of these technologies has failed to improve the Ergonomic load on the postural behavior of the clinicians, which leads to occurrences of WMSDs. Figure 3 presents a summary of the discussion and details the ergonomic issues in general dentistry and methods employed to resolve these issues.

Dentists are thus at high risk of developing WMSDs, and the design-redesign of the dental chair is incapable of solving the problem. RULA-based studies prove that immediate and necessary actions and changes are needed in this context. Preventive measures in the current scenario are primarily dependent on awareness of the dentist and their ability to avoid prominent drawbacks, such as postures and isometric work conditions.

## Risk assessment of dental work environment

To strengthen our understanding of the subject matter and consolidate the findings of the review, we conducted a subjective survey in a public hospital*. The primary objective was to study the interactions of the dentists with their workspace and analyze the associated risks.

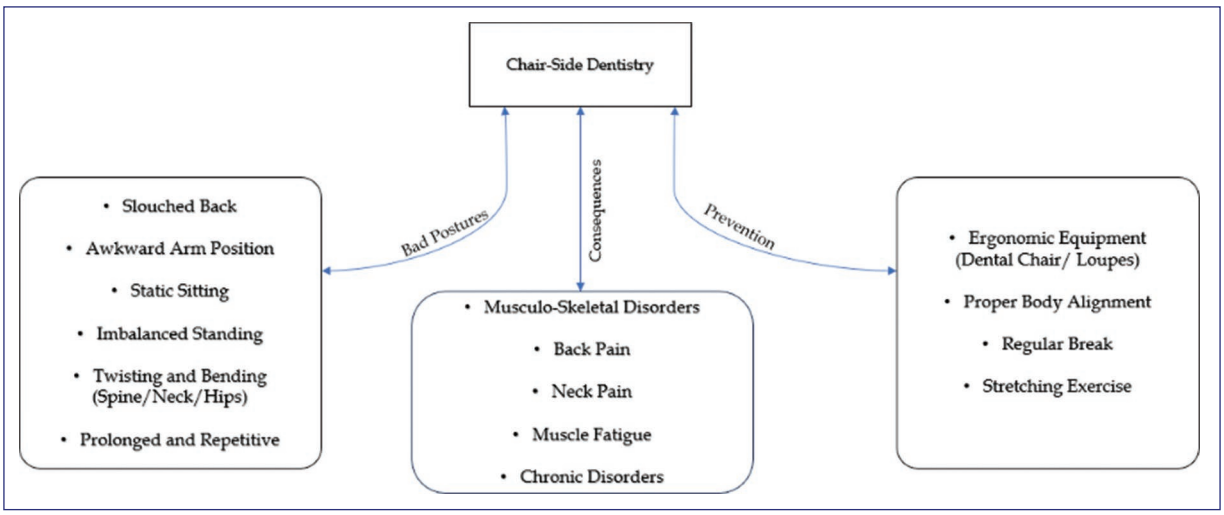


**Figure 3.** Prominent postural issues in general dentistry, their expected consequences, and popular preventive measures.

## Survey design

The survey was designed based on subjective questions addressing various aspects of muscle fatigue and workload experienced by dentists as reported in the literature and identified from visual inspection. The online questionnaire had twenty questions with a 5-point Likert Scale response option. Before conducting the survey, a pretest survey was floated in online mode to practicing dentists in India randomly. Eleven subjects participated in the survey (not included in the main survey) from different parts of the country. The responses were recorded in the Google Cloud. The survey was validated by two subject matter experts with more than 20 years of clinical and academic experience, as suggested in the Delphi technique. Based on the suggestions, the questionnaire was modified for clarity and misinterpretation possibilities.

A total of 30 subjects (n = 30, 19 Females, 11 males) with an average age of (25.9 ± 3.12 years) and an average work experience of (1.87 ± 1.49 years) participated in the survey. However, the sample size is limited both in terms of the number of subjects and geographical monotony, but as reported in[36-38] and as suggested in statistical methods, a random sample of 30 subjects is considered to be sufficient in expanding the results.

The questionnaire aimed at extracting the perception of dentists about their workspace. The survey emphasized the association/attitude of dentists with their interactions with the dental tools, workstation, and office space. Different key elements of the dental workspace were identified from the literature and by questioning the experts. The dentists were asked both behavioral and qualitative questions about their interactions with these key elements. The aim was to identify the risks associated with these interactions. The questions were designed to obtain information about both the probability of the risk and its severity. The entire procedure (written in generic form for all the practitioners) was divided into elementary processes and events.

## Risk assessment

For risk assessment, the participants were asked to rank different processes and events based on a 5-point Likert Scale, probability of occurrence from 1 to 5, where 1 is the least probable, and 5 is the highest. Similarly, for each such event, the risks were formulated, and the participants were asked to rank the severity of such a risk from 1 to 5, wherein 1 is the least hazardous and 5 is catastrophic. Table 3 shows the color map of the risk assessment matrix.

The average scoring of all the participants was done to compute the individual score of likelihood and consequences for all the elements of risk. For fractional outputs, the digit was rounded off to the nearest integer. The overall Risk Score is calculated as the product of likelihood and consequences.

The risks associated with arm operations are very high, which attributes to high risks in postural compromise and interactions with different tools used of which is a major in chair-side dentistry.

This high risk is associated with the occurrence of muscle fatigue in the operative arm of dentists.

**Table 3.** Risk assessment in dental clinics and severity of various subactivities

| Risk | Likelihood (L) | | | | | Consequences (C) | | | | | Risk score (L*C) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1-5 | 6-10 | 11-15 | 16-20 | 21-25 |
| Foot operations | | | | | | | | | | | | | | | |
| Arm operations | | | | | | | | | | | | | | | |
| Postural compromise | | | | | | | | | | | | | | | |
| Interactions with tools | | | | | | | | | | | | | | | |
| Bio-Hazards | | | | | | | | | | | | | | | |

| Color map | Score | Risk score | Interpretation |
|---|---|---|---|
| | 1 | 0-5 | Insignificant |
| | 2 | 5-10 | Minor |
| | 3 | 10-15 | Moderate |
| | 4 | 15-20 | Major |
| | 5 | 20-25 | Catastrophic |

The risk score is the product of Likelihood (L) and Consequence (C). The * indicates the multiplier.

Furthermore, there is sufficient evidence for the development of chronic disorders resulting from awkward postures. As per the discussions on Risk Assessment, any risk greater than or equal to moderate should be addressed for sustainable solutions. There are limited risk assessment studies in dentistry, the majority of which focus on procedure-related injuries in the oral cavity of the patient. None of the risk assessment strategies has been worked upon for the workspace design of dental offices and addressing occupational hazards in dentistry. The upper limbs of dentists are at a higher risk, and the risks increase with people of greater height.

The combined effect of excessive workload and Postural disintegration leads to worse effects on dentists practicing General Dentistry. Preventive measures are more subjective, suggestive, and less technological. The impact of redesigning dental chairs for ergonomic usage has no significant effect on the process, and Rapid Upper Limb Assessment (RULA) studies suggest major procedural changes in the setup of dental clinics.

## Results and discussions

General dentistry suffers from a severe risk of WMSDs, even though the popular remedies are suggestive and advisory. No major study is found in the literature that accounts for developing corrective or alert remedies for dentists about poor postures. However, advisories and training programs are not sufficient for serving the purpose[36].

We instead investigated the application of technological remedies in solving postural issues in other stressful work environments, such as other medical professionals, industrial setups, agriculture, and assembly lines. As a common trait, technological interventions for postural improvement are based on three major principles of physical ergonomics that consider anthropometry, biomechanics, and workload[39]. Thus, similar technologies can be broadened and customized for use according to specific workspaces.

Based on the available literature, the technological interventions, as said, can be classified into two major groups: corrective and alert systems. Wearable technologies are at the center of development in both groups. They function on real-time biomechanical feedback for ergonomic conditioning[40]. In a group of medical staff nurses, the monitoring of posture was done using smart wearable garments embedded with sensors and a smartphone application. The application would alert the nurses about holding a poor posture for long hours[41]. In a similar work, an inertial sensor-based wearable device was used to generate alerts for bad postures[42]. While

the use of motion sensors at different regions of the body, along with surface EMG to measure the real-time fatigue and alert the user, proved beneficial[37].

Assistive devices are found to be of help in solving the postural risks in many work environments. However, these technologies are not free from drawbacks, but to a large extent, help the workforce in better executing routine activities. Archelis is one commercially available exoskeleton suit designed for surgeons in the laparoscopic workstation[43,44]. The exoskeleton devices essentially are combinations of mechanical linkages with added support in the target areas. Based on the design, they aim at establishing a harmony between mechanics and user comfort[45]. Properly designed and implemented exoskeleton suits can help reduce muscle fatigue by nearly 61% and provide flexion support[46].

Apart from wearable devices, robot-guided systems and automated mechanisms (conveyor belts) are also reported to be helpful in some cases, reducing ergonomic load on the staff[47]. A guided high definition imaging system (exoscope) providing visualization on a comfortable monitor helped in maintaining the neutral head posture and body alignment during anterior cervical surgery[48]. Collaborative robots (COBOTS) are being prominently used in industry now, and designing protocols by employing ergonomic principles can help in reducing muscular fatigue. They can serve as an assistant and share the manual load, relieving the workforce of painful tasks[49].

## COBOT: future scope in general dentistry

Applications of robotic technology have been widely explored in healthcare and medicine. The classification of medical robots ranges from very sophisticated surgical and rehab robots to logistic managers such as delivery and disinfection agents. The Da Vinci system is the state-of-the-art surgical system that is being used as a benchmark from its inception[50]. Surgical robots are very popular and well established in treating gastro and orthopedic procedures[38,51]. However, these systems are studied and developed on the lines of engineering accuracy and precision as a primary aim, and user interaction is not a design factor.

Industry 4.0 and smart manufacturing technology have led the way to a very interesting subject of human–machine interaction (HMI). COBOTS, as a result, have been widely used in stressful work conditions. The application of COBOT in surgical procedures is found in a few reports, which emphasize the safety and sustainability[52]. The principles of HMI are human-centric, and the use of COBOT improves the dexterity and visualization for surgeons, along with high procedural accuracy and precision[53-55].

Interestingly, dentistry is not developed in an isolated fashion and is teleoperated, and COBOTS have been developed for dental procedures. Oral Surgical Robots, however, are limited only to Implantology. YOMI Robot is a commercially available system that is a state-of-the-art machine in dental implants[56]. COBOT in oral procedures can be used for improving muscle fatigue, constrained visibility, and postural misalignment in professionals owing to work requirements[57]. A consolidated report of the major papers cited in this article is listed in table 4.

A collaborative robot suiting the needs of Dentists and Hygienists working in General Dentistry can be designed using principles of Physical Ergonomics and HMI. The system predominantly consists of an adjustable chair suited for the dentist with sufficient leg space. A display unit at a sufficient angle and distance to view the oral cavity. A primary COBOT arm in comfortable hand motion placement. The end effector of the COBOT is essentially a detachable dental tool and a monocular vision system (high-quality camera to view the oral cavity). Figure 4 depicts a conceptual setup for COBOT-assisted oral cavity examination.

### Technical specifications of the collaborative platform for general dentistry

COBOTS are highly effective in precise control, and their capabilities in load sharing are often highly suitable for repetitive and labor-intensive work. In general dentistry, the customization of COBOT assisted with HMI principles can be very effective in reducing muscle fatigue and improving postural ergonomics. Figure 5 below represents a functional block diagram of the system.

Since the major applications in the general dentistry pertain to tasks such as drilling, scaling, cleaning, and examination, the application of the COBOT can be controlled in two possible modes, manual and shared control. The system architecture is detailed in table 5.

### Application scenarios and COBOT usage in general dentistry

The load on general dentistry is immense, as established in this research and other previous works. The common practices include examination, cleaning, scaling, cavity preparation, and drilling. We elaborate here in this section on two major procedures: cavity preparation and ultrasonic scaling assisted by COBOT.

**Table 4.** Summary of selected prominent papers included in the literature survey

| No. | Author and year | Abstract summary | Addressed technology |
|---|---|---|---|
| 1. | Ahearna et al., 2009[20] | Discusses principles of ergonomics for the design of the workspace. Identifying integration of technology with the dental workstation is a challenge | Principles of ergonomic design. No quantitative review of the assessed method is discussed |
| 2. | Younis et al., 2022[26] | Online survey with 600 participants. The results establish that around 87% of the practicing dentists are affected by some sort of MSDs | Statistical methods. Subjective suggestions such as maintaining neutral postures and work breaks |
| 3. | Abichandani et al., 2013[28] | Emphasizes the prevalence of Carpal Tunnel Syndrome in dentists | Review of articles does not propose any remedial method |
| 4. | Rafie et al., 2015[29] | Experimental study to analyze the threat of MSDs. Identifies more than 80% of the subjects under severe effect | Rapid Upper Limb Assessment (RULA)/Nordic Musculoskeletal Questionnaire (NMQ)/Statistical Tests |
| 5. | Bedi et al., 2015[31] | Subjective questionnaire to study the MSDs in dentists. Identifies wrist and back as potential threat areas | No potential solution was discussed |
| 6. | Faust et al., 2021[32] | Random case study in undergraduate dental students to assess the ergonomic improvements post-ergonomic training | Reports on postural ergonomic improvements by mapping shoulder abduction position and spinal flexion after proper training. |
| 7. | Li, 2024[50] | Explores the common robotic devices used in healthcare applications | Review of rehabilitation, surgical, and healthcare robots. Does not include dentistry |
| 8. | Lu et al., 2024[55] | Introduces a serial-parallel hybrid robot for addressing the high forces required in surgeries | Precision control of surgical robots in orthopedic surgeries |
| 9. | Bolding and Reebye, 2020[56] | Introduces Robotic Guided Implants using Yomi Robot | Addresses haptic feedback and robotic systems for dental implants and improvements in the accuracy over conventional surgeries, but does not list the ergonomic improvements |
| 10. | Bahrami et al., 2024[57] | Review of Robot-Assisted Oral Implants | Review of the accuracy and precision of Robotic Devices used for Implantology |

## Cavity preparation

Cavity preparation starts with the identification of carious lesions. Intraoral scans and CBCT scans can be used to design the three-dimensional point cloud of the lesions and identify the depth of cavities. Depending on the mode of operation, high-speed tools mounted on the COBOT can then be employed for performing the drilling tasks. The drilling force can be guided by the COBOT shared interface. This design method incorporates the haptic force feedback for managing both the soft tissues and the hard bones.

## Ultrasonic scaling

Scaling is a repetitive task requiring a lot of cognitive and physical load on the dentists. The COBOT in shared control mode can be assigned preplanned trajectories extracted from recorded scans by planning software. For calculus removal, the maximum load requirement may vary up to 5N, which can be corrected in real-time based on the haptic feedback from the Load/Torque sensors incorporated in the scaling tool.

Applications of this COBOT platform can be extended to other activities and procedures in General Dentistry, and based on the specific requirements, the tools and feedback sensing mechanisms can be customized.

## *Future research and experimental validation*

The design of the workspace, incorporating a six-axis collaborative robot arm in the vicinity of the dental chair, requires careful adjustment of Ergonomic and Engineering principles. Safety and compliance should be prioritized, ensuring high accuracy and precision of maneuver. Position control of the tool is a challenging task, given the complex design of the human oral

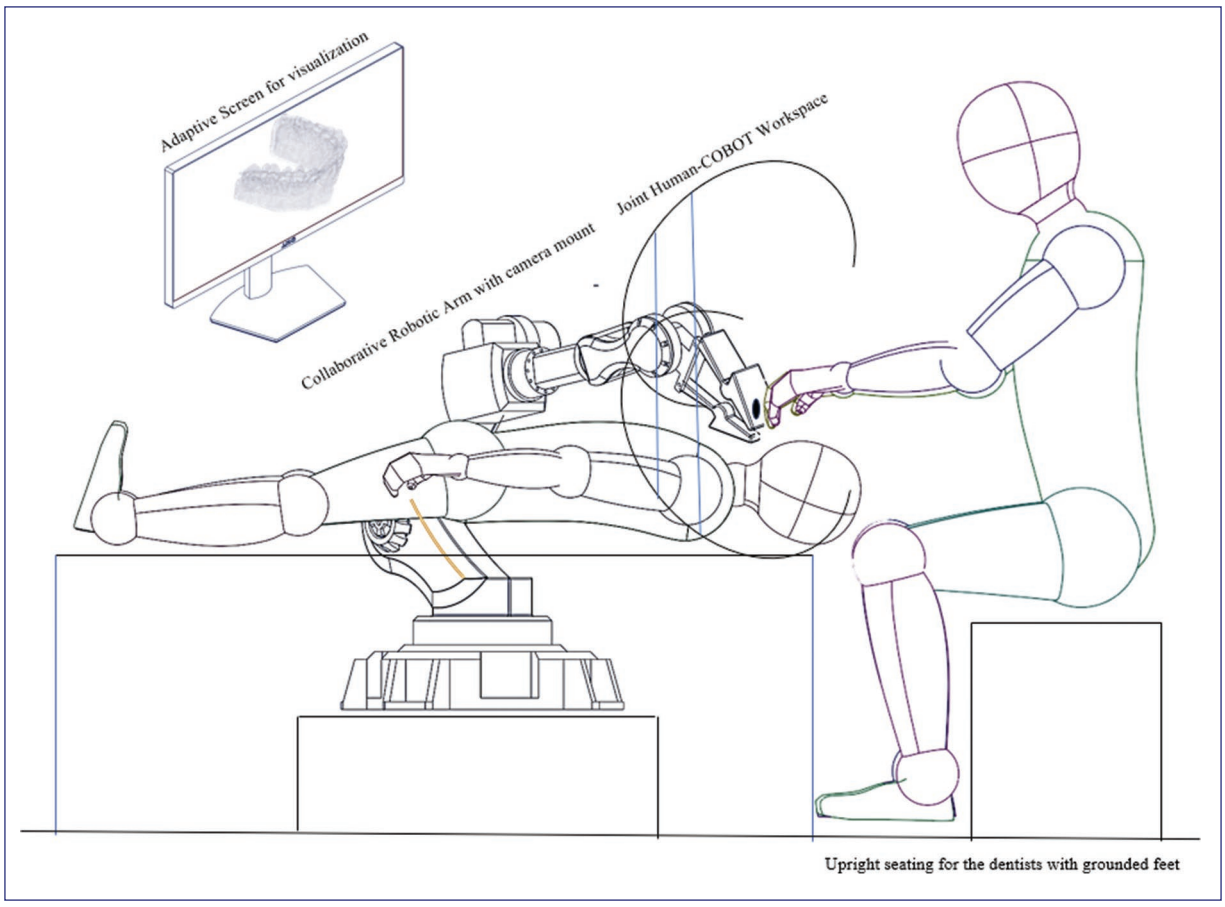


**Figure 4.** Proposed framework using a collaborative robot in dental clinics.

**Table 5.** Critical components and specifications of a collaborative robot platform for general dentistry

| No. | Component | Classification | Specification |
|---|---|---|---|
| 1. | Collaborative robot arm | Hardware | 1. A six-axis robotic arm with a payload capacity of up to 1 KgF (low for handling oral surgical tools such as drills and scalers).<br>2. To maintain the rigidity of the system ground-mounted design should be effective.<br>3. A dexterous and maneuverable end Effector to address the complex oral geometry.<br>4. The reach of the robotic arm may range from 500-750 mm so that it can be comfortably placed near the dental chair.<br>5. The point-to-point trajectory repeatability must be within a 0.5 mm range to manage precision. |
| 2. | End effector | Hardware | 1. Easy swap press fit tool design to maximize operability and maintain sterility.<br>2. Integration of irrigation and suction mechanism.<br>3. High-speed drives for drilling tasks.<br>4. Integrated force feedback mechanism in the tool for calibrating the haptic interface. |
| 3. | Feedback mechanism | Hardware and software | 1. Vision feedback using high-stability and auto focus cameras for consistent indirect viewing.<br>2. Haptic controllers at the dentist's hand to map the force feedback from the end effector load sensors. |
| 4. | Operational control | Software/ algorithms | 1. Manual mode:<br>a. Low impedance operation for easy maneuver and safe operations.<br>b. Quick response controls in the Graphical User Interface (GUI) for safety stops.<br>2. Shared control mode:<br>a. Design preoperative trajectory based on scans.<br>b. Angular torque compensation for High Impedance Force feedback to stop motion beyond the planned trajectory. |

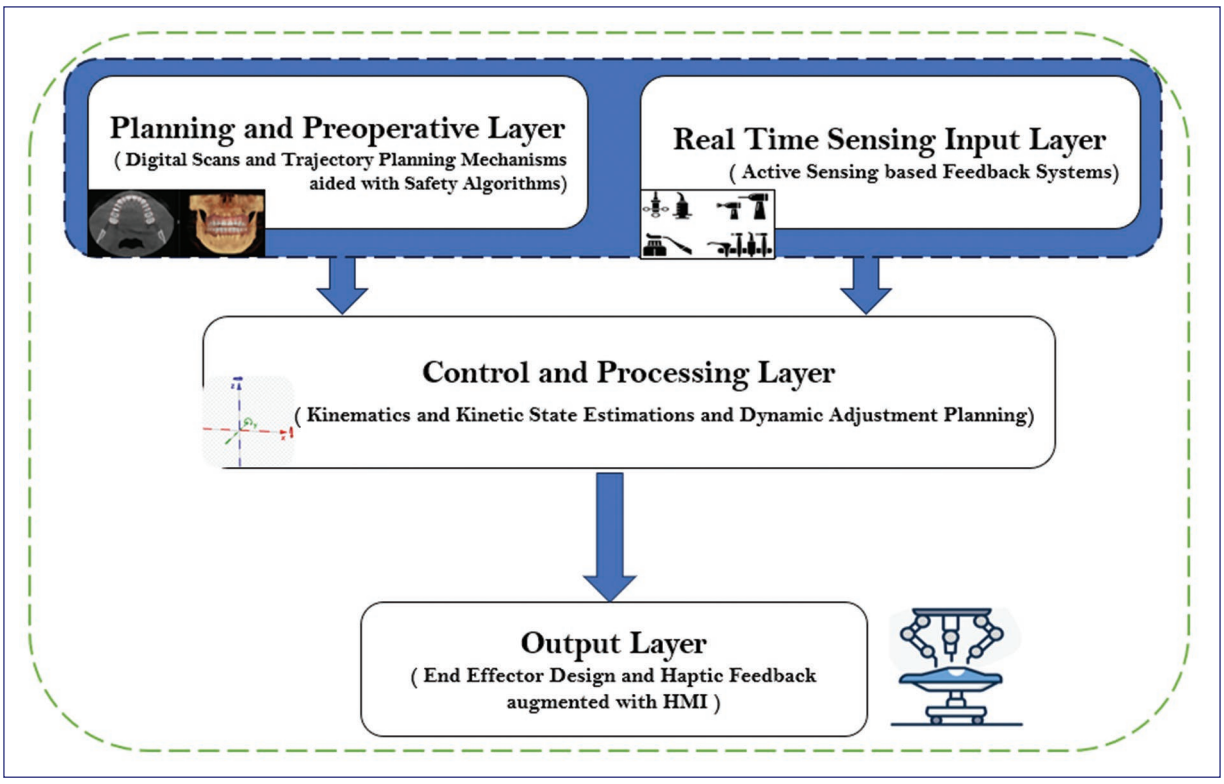


**Figure 5.** Functional block diagram of a collaborative robot-assisted dentistry.

cavity. Haptic feedback from the tool must be calibrated with high sensitivity because of the presence of both soft tissues and hard enamel in the near vicinity. Reaching the extremities of buccal teeth is a design challenge for optimizing the tool size. However, high computation systems are available, catering to the latency delays in shared control processes, which must be seriously managed.

In this study, we did not find, to the best of our understanding, any previous research that caters to the improvement of postural ergonomics in dentistry using robotic devices. Hence, benchmarking the design shall be a challenge and needs validation protocols using laboratory testing supplemented with clinical trials.

## *Limitations of the study and protocols*

The sample size of the survey was limited to thirty subjects in India. The variations in the clinical practice and usage of advanced tools might vary in different workspaces and regions. However, the study reveals that the problem of Workload and Postural Ergonomics has been consistent and extensively researched upon in different parts of the globe.

The use of technologies with an ergonomic perspective is very limited and often indicative. Predominantly, the use of Wearable and exoskeletons is explored and reported. Exosuits, on one hand, offer stress relief; on the other hand, they suffer from fundamental issues of stability and user interactions because of their intrinsic weight. However, they provide good support to lower limbs; they do not solve the primitive design issue of indirect viewing of the oral cavity. Thus, we conclude that the use of technology to solve the issue of postural ergonomics in general dentistry is insufficient, ineffective, and scattered. We propose a conceptual design of a collaborative robotic platform for performing routine day-to-day activities in general dentistry. The concept employs the principles of ergonomics and design paradigms supported with engineering control theory for relieving dentists' trauma.

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CASE REPORT

# Severe thiamine-remitted ifosfamide encephalopathy: a case report and a literature review

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## Abstract

*Ifosfamide encephalopathy is a serious and potentially fatal adverse reaction that occurs in some patients receiving cytostatic therapy with this drug. It is characterized by a progressive deterioration of the baseline neurological state, depends on the dose and limits antineoplastic treatment. We present the case of a 21-year-old woman diagnosed with primary synovial sarcoma of the neck, progressing from the first relapse. At the end of ifosfamide administration (weight-based dose of 3 g/m²/dose, administered as a 3-hour infusion), with a total cumulative dose of 66 g/m², she presented the sensation of depersonalization, accompanied by significant anxiety, sialorrhea, paresthesias and constant myoclonus in the upper extremities, progressing in the following 18 hours with motor aphasia, disorientation, apraxia, dysmetria, decreased strength (which made it impossible to hold the head, sit and stand), hyperreflexia, global aphasia, apathy and stupor. Four doses of 100 mg of intravenous thiamine were administered, infused for 10 minutes each dose, every 4 hours. The neurological deterioration remitted progressively and completely, without recurrence of symptoms and without adverse reactions. Thiamine has been shown to be effective in the treatment of ifosfamide encephalopathy. The usual dose is 100 mg every 4–6 hours intravenously.*

***Keywords:*** *Encephalopathy. Ifosfamide. Thiamine. Methylene blue. Sarcoma. Cancer.*

## Introduction

Ifosfamide encephalopathy is a serious, potentially fatal adverse reaction that occurs in some patients receiving cytostatic therapy with this drug; It is characterized by a progressive deterioration of baseline neurological status[1], is dose-dependent, and limits antineoplastic treatment.

Ifosfamide is a cytostatic drug belonging to the alkylating agent family. It is used in the treatment of multiple malignancies in both adults and pediatric patients, including carcinomas, sarcomas, and lymphomas[2]. It induces its action through the alkylation of DNA (deoxyribonucleic acid), causing intra- and inter-chain breaks[3]; the parent drug is converted to the active metabolite 4-hydroxy-ifosfamide and several inactive metabolites through the cytochrome pathway[3]; chloroacetaldehyde (inactive metabolite) is lipophilic and freely crosses the blood–brain barrier, causing different neurotoxic alterations, collectively called ifosfamide encephalopathy[3].

The formation of chlorethylamine (another inactive metabolite) indirectly favors neurotoxicity through the inhibition of mitochondrial flavoproteins, causing accumulation of nicotinamide adenine dinucleotide and decreased elimination of chloroacetaldehyde[4].

Ifosfamide encephalopathy develops in 10-60% of patients receiving this drug[2-4] (in pediatric patients, only in 2-5%[5,6]); it is a dose-dependent adverse reaction[4], and occurs when the cumulative dose is > 60 g/m²[2], in most cases[7].

Risk factors include short drug infusion time, hypoalbuminemia, hyponatremia, pre-existing kidney injury,

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history of nephrectomy or brain metastases, history of radiation to the central nervous system, previous use of cisplatin, and sarcoma as a baseline diagnosis[3,4].

The clinical picture is characterized by confusion, disorientation, agitation, drowsiness, hallucinations, mutism, psychosis, asterixis, and other extrapyramidal symptoms, hemiballism, and convulsions, and may progress to coma and death[4,5,8,9]. It develops between 2 and 48 h after drug administration[4]; however, cases of patients presenting it up to 14 days after administration have been reported[10].

Encephalopathy remits spontaneously 48-72 h after stopping the drug; however, in a considerable group of patients, neurological deterioration progresses to coma and death[4].

We report the present case with the aim of highlighting the efficacy of intravenous thiamine in the complete reversal of ifosfamide encephalopathy, as an alternative to methylene blue for the treatment of this complication.

## Case report

A 21-year-old woman was diagnosed with primary synovial sarcoma of the neck, progressing from the first relapse. The primary disease was treated with subtotal resection, ifosfamide-doxorubicin (six cycles) and radiotherapy, subsequently, it relapsed to the upper mediastinum after 2 years and 6 months of surveillance, receiving treatment for relapse with vincristine-carboplatin-epirubicin (six cycles), total resection and radiotherapy, however, the neoplasm progressed to the pericardium and posterior mediastinum, so treatment was initiated with subtotal resection and ifosfamide-doxorubicin (one cycle until before encephalopathy event). At the end of the administration of the first dose of ifosfamide of the second cycle (weight-based dose of 3 g/m$^2$/dose, administered as a 3-h infusion, and a total dose per cycle of 9 g/m$^2$), having a total cumulative dose for this drug of 66 g/m$^2$, she presented a feeling of depersonalization (referred by the patient as not feeling herself), accompanied by significant anxiety (referred by the relative), sialorrhea, paresthesias and constant myoclonus in the upper extremities. Progressing in the following 18 hours with motor aphasia, disorientation, apraxia, dysmetria, decreased strength (which made it impossible to hold the head, sit and stand), hyperreflexia, global aphasia, apathy and stupor. Sodium was 147 mEq/L, potassium at 2.9 mEq/L, and creatinine at 1.14 mg/dL, with no other alteration in blood chemistry or blood count; plain head tomography with cortical atrophy, with no evidence of hemorrhage, metastasis, or indirect data of ischemia; Electroencephalogram with mild generalized dysfunction, with a predominance of theta waves. Four doses of 100 mg of intravenous thiamine were administered, infused for 10 min each dose, every 4 h; 3 h after the first dose, the neurological deterioration progressively and completely subsided, without recurrent symptoms and without adverse reactions, highlighting only the amnesia of the last 36 h (Fig. 1 describes the clinical evolution chronologically).

## Discussion

The diagnosis of ifosfamide encephalopathy was established by the exclusion of other differential diagnoses (brain metastasis, status epilepticus, significant metabolic alterations, intracranial hemorrhage, and cerebral ischemia), by the history of the cumulative dose of ifosfamide, as well as by the temporal relationship between the onset of symptoms and the administration of the drug.

Methylene blue was historically used in the treatment of ifosfamide encephalopathy; it is thought to inhibit the formation of chloroacetaldehyde through the blockade of extrahepatic monoamine oxidases, and to block the inhibition of mitochondrial flavoproteins by chlorethylamine; however, its benefit is questionable[4].

Thiamine has been proposed as an alternative treatment to methylene blue in patients with ifosfamide encephalopathy[4,9,11]; it has shown benefit even in patients who develop this neurotoxicity without having identifiable risk factors[11].

The usual dose of thiamine is 100 mg every 4-6 h intravenously, infused for 10 min each dose, until recovery of baseline neurological status[9,12], generally occurring over the course of 10-30 h[9,12,13].

The progressive improvement that our patient showed after just 3 h of the first administration of thiamine stands out, which contrasts markedly with what has been described in the literature (between 10 and 30 h after starting the administration).

The usefulness of thiamine, albumin, and methylene blue as prophylaxis for the development of encephalopathy has been the objective of different clinical trials; however, the results do not support their routine use because they do not reduce the risk of developing neurological deterioration[3,4,14,15].

In our patient, remission of neurological deterioration began 3 h after the first dose of thiamine was administered, and resolved completely after four doses. The risk factors identified for neurotoxicity were only the cumulative dose of the drug and kidney injury. Clinical

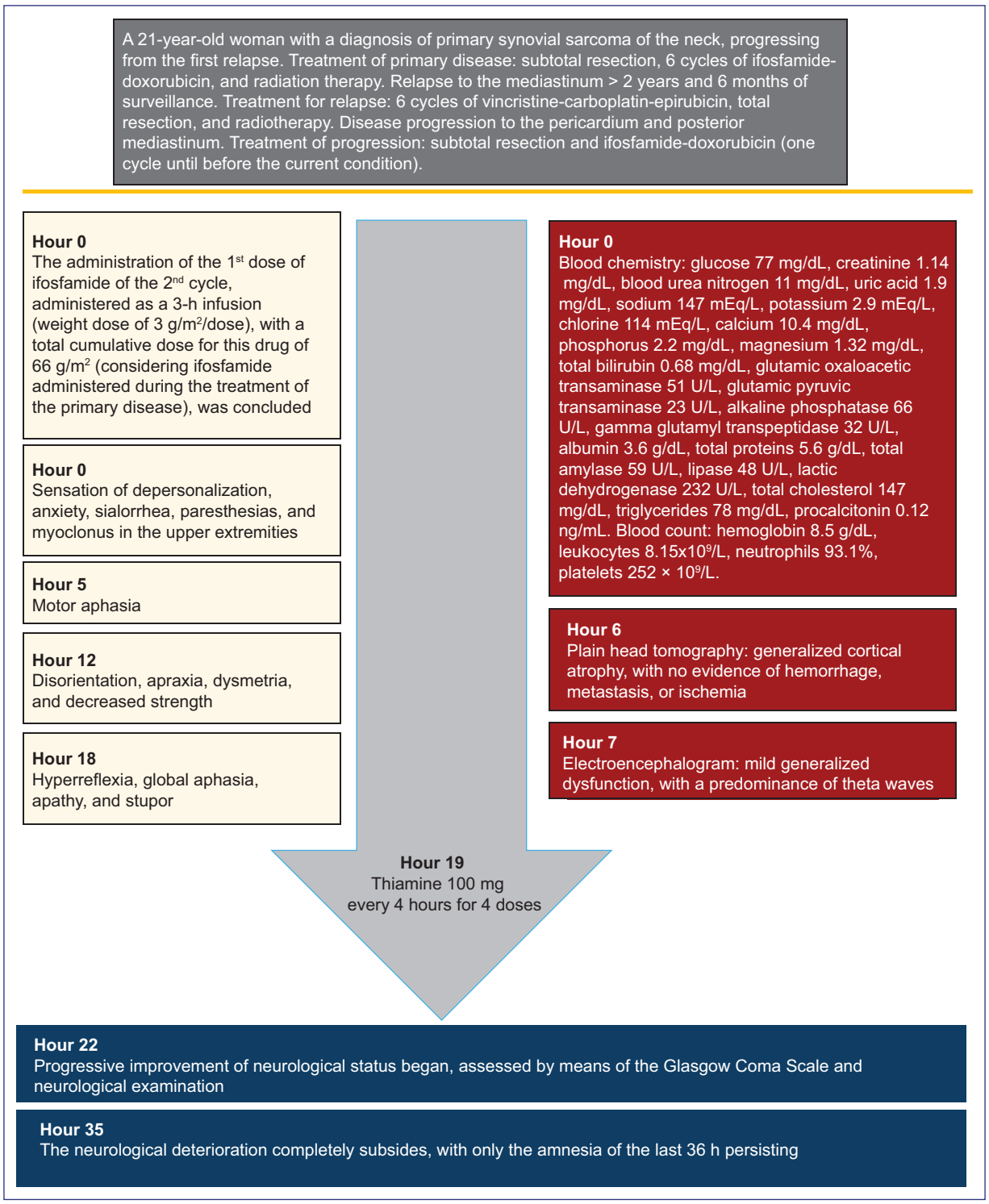


**Figure 1.** Chronological sequence of clinical evolution.

improvement was manifested rapidly, and no adverse reactions were identified.

For the treatment of ifosfamide encephalopathy in our patient, thiamine was chosen instead of methylene blue, due to the greater accessibility in obtaining it and its low cost.

The patient requested a change to another line of treatment that did not include ifosfamide, so 1 month

later, treatment with gemcitabine-docetaxel was started, receiving three cycles on an outpatient basis; however, the disease progressed in the mediastinum and pleural cavities, dying at home with comfort treatment 6 months after the encephalopathy event. It should be clarified that the amnesia described in the presentation of the case was permanent and retrograde; there was no recovery of the lost memories. However, after the administration of thiamine, he recovered the mental function for the creation of new memories.

The molecular mechanism by which thiamine reverses ifosfamide encephalopathy is unknown[3,4]. Thiamine acts as a cofactor for transketolase, α-ketoglutarate dehydrogenase and pyruvate dehydrogenase complex; it is involved in glucose metabolism, energy generation and nucleic acid synthesis, so its deficiency results in mitochondrial dysfunction, reduction of pyruvate oxidation, lactate accumulation, decrease in pH and acidosis, reduction in the production of adenosine triphosphate, thymidine diphosphate (TDP), and thymidine triphosphate (TTP), oxidative stress, myelin sheath damage, impaired nerve conduction, neuronal death, and neurological deficits[3,16]. It is speculated that thiamine administration promotes the functioning of TDP and TTP-dependent enzymes, reversing the neurological deterioration associated with ifosfamide infusion[3].

Further pre-clinical studies are needed to clarify the pharmacodynamics of thiamine in the treatment of ifosfamide encephalopathy. Although the case we present was successful, it is necessary to increase clinical evidence in order to establish defined therapeutic guidelines.

The Research and Research Ethics Committees of the Hospital Juárez de México granted a total waiver of consent due to the retrospective nature of the study, in accordance with current Mexican laws.

## Conclusion

Thiamine has been shown to be effective in the treatment of ifosfamide encephalopathy. The usual dose is 100 mg every 4-6 h intravenously.

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## Conflicts of interest

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## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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BRIEF REVIEW

# Exploring the role of glycine: modulation of gene expression of GPR3, GPR6, and GPR12 in astrocytes and its potential implication in the pathogenesis of Alzheimer's and beta-amyloid accumulation

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## Abstract

*Astrocytes, a subtype of glial cells prevalent in the central nervous system, are characterized by two principal types: protoplasmic, primarily located in gray matter, and fibrous, predominantly found in white matter and the optic nerve. Protoplasmic astrocytes extend end feet toward blood vessels in the gray matter, forming the glial limiting membrane, whereas fibrous astrocytes in the white matter display smaller somata with straight, non-branched processes. These cells play a pivotal role in maintaining redox potential, regulating neurotransmitter and ion concentrations, and eliminating toxins from cerebrospinal fluid. In addition, astrocytes can modulate neuronal activity by influencing intracellular Ca2+ concentrations and releasing gliotransmitters. Glycine has an important role in the modulation of the orphan receptors GPR3, GPR6, and GPR12. In conclusion, glycine helps in the modulation of the amyloid beta pathway, as established in the anti-inflammatory properties of glycine and its relationship with the GPR3, GPR6, and GPR12.*

***Keywords:*** *Alzheimer. Astrocytes. Glycine. Orphan receptors.*

## Introduction

The astrocytes are a subtype of the glial cells that are the majority of cells in the central nervous system (CNS)[1]. There are two main types of astrocytes: protoplasmic and fibrous. Protoplasmic astrocytes are found in the gray matter, and they have the main function of extending endfeet to blood vessels and enwrapping them to form the glial limiting membrane[2]. Fibrous astrocytes are found in the white matter and in the optic nerve; they have smaller somata and straight, non-branched processes. They also have contact with blood vessels and create a perivascular or subpial endfeet[3]. They have a higher expression of an intermediate filament protein with the name of glial fibrillary acidic protein (GFAP)[2]. The astrocytes have multiple functions associated with neuronal functions; they maintain the redox potential, regulate neurotransmitter and ion concentrations, and remove toxins and debris from the cerebrospinal fluid[4]. Astrocytes have activity to increase intracellular Ca2+ concentrations and the release of signaling gliotransmitters to excite neurons or other astrocytes[5]. γ-aminobutyric acid type A (GABAA) receptors, the principal inhibitory neurotransmitter receptors responsible for rapid inhibition in the basal ganglia, are receptors assembled as pentameric structures of subunits, featuring a central Cl–permeable pore[6]. Suppresses the activity of signal-receiving neurons through interaction with the GABAA receptor located

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on these cells. The GABAA receptor is a channel-forming protein facilitating the influx of chloride ions into the cells[7]. Dopamine (DA) serves as a vital neurotransmitter in diverse brain functions, including motor control and motor learning[8]. Reports indicate DA release and dopamine receptor (DA-R) activity in the cerebral cortex and various other regions[9]. The activation of DA-R in astrocytes could potentially lead to gliotransmitter release following an elevation in intracellular Ca2+ levels in D1 receptor[10].

## The DA-R are located and encoded by different genes

D1 receptor (D1R) encoding is by the gene 5q31-q34 in humans. The D2 receptor (D2R) and D4 receptor (D4R) are on chromosome 11th, the D3 receptor is located on the third chromosome, and the D5 receptor is on the fourth chromosome[11].

Reduced expression levels of DA-R1 and R2 in the hippocampus have been reported in Alzheimer's disease (AD) patients compared to controls[12]. D1R is coupled to a GPCR that is expressed in the midbrain and forebrain, regulating motor behavior, reward, motivational states, and cognitive processes[13]. D2R is related to regulating the activity of DA neurons and controls the synthesis, release, and uptake of DA[14].

### *AD*

AD is a progressive brain disorder that affects memory, cognitive abilities, and thinking skills[15,16]. When the disease is developing, the connections between neurons and the glial cells are breaking down, and slowing[17].

Some of the signs that patience with AD presents are:

– A difference in common behavior
– Increase sleeping
– Seizures
– Difficult to speak and write
– Loss of memory[17]

The AD produces a hypertrophic appearance in the astrocytes, and these astrocytes are associated with cytoskeletal proteins, such as GFAP and vimentin[18]. One of the reasons for neurodegenerative diseases is a protein called amyloid β (Aβ). This protein has a central role in AD and comes from the amyloid protein precursor (APP)[6]. This type of dementia can also be because of a mutation in this gene (APP)[19]. APP is a single membrane-spanning domain, a large extracellular glycosylated N-terminus, and a shorter cytoplasmic C-terminus. It has several different isoforms, ranging in size from 695 to 770 amino acids[20]. Aβ produces an inflammatory response that activates microglia, and the primary inflammatory cells of the CNS release inflammatory mediators[21]. The exact physiological functions of Aβ remain unknown, but some studies have shown a relationship between Aβ and the pathogenesis of AD[22]. The Aβ removal is dependent on the proteolysis and lysosome degradation system. The oligomers and deposits of this protein are the ones that give the neurotoxicity[23]. A study in StatPearls confirms that Aβhas been detectable in living people for over a decade, but more concentrations are found in older people[7]. The deposits of Aβ are produced in part in the brain parenchyma and in the walls of blood vessels. It is also noticed that the neprilysin and scavenger receptor Class B member 1 gene expression in astrocytes exposed to Aβ is expressed, but in people with AD, there is no expression of these receptors[17].

There are two major isoforms of Aβ, Aβ42 and Aβ40. The only difference between Aβ42 and Aβ40 is that Aβ40 does not have two extra residues at the C-terminus. In AD patients, the plaques are mostly Aβ42, and some plaques contain only Aβ42, even though Aβ40 concentration is several-fold more than Aβ42, caused by the activity of the enzyme γ-secretase[24].

The amyloidogenic pathway of the APP protein starts with the transmembrane APP25. The transmembrane APP[25] undergoes an initial proteolytic cleavage by the β-secretase enzyme, generating a soluble fragment called sAPPβ and C99, due to its length of 99 amino acids, a fragment that keeps embedded in the membrane. The last is the cleavage of C99 by the γ-secretase enzyme, which makes two fragments: the AICD and the Aβ peptide[26] (Fig. 1).

### *Clinical studies*

Clinical trials of early or preventive interventions based on amyloid/tau theory and those targeting other pathophysiology are ongoing or have been initiated. Many ongoing clinical trials on AD are focused on disease-modifying therapies that target the causes and can change the course of AD[27].

– Aducanumab, a human-derived antibody targeting Aβ, aducanumab binds to a linear epitope formed by amino acids 3-7 of the Aβ peptide. Aducanumab discriminates between monomers and oligomeric or fibrillar aggregates based on weak monovalent affinity, rapid binding kinetics, and strong avidity for epitope-rich aggregates[28].
– Varoglutamstat (PQ912) is a glutaminyl cyclase inhibitor that reduces pGlu-Aβ generation. Glutaminyl

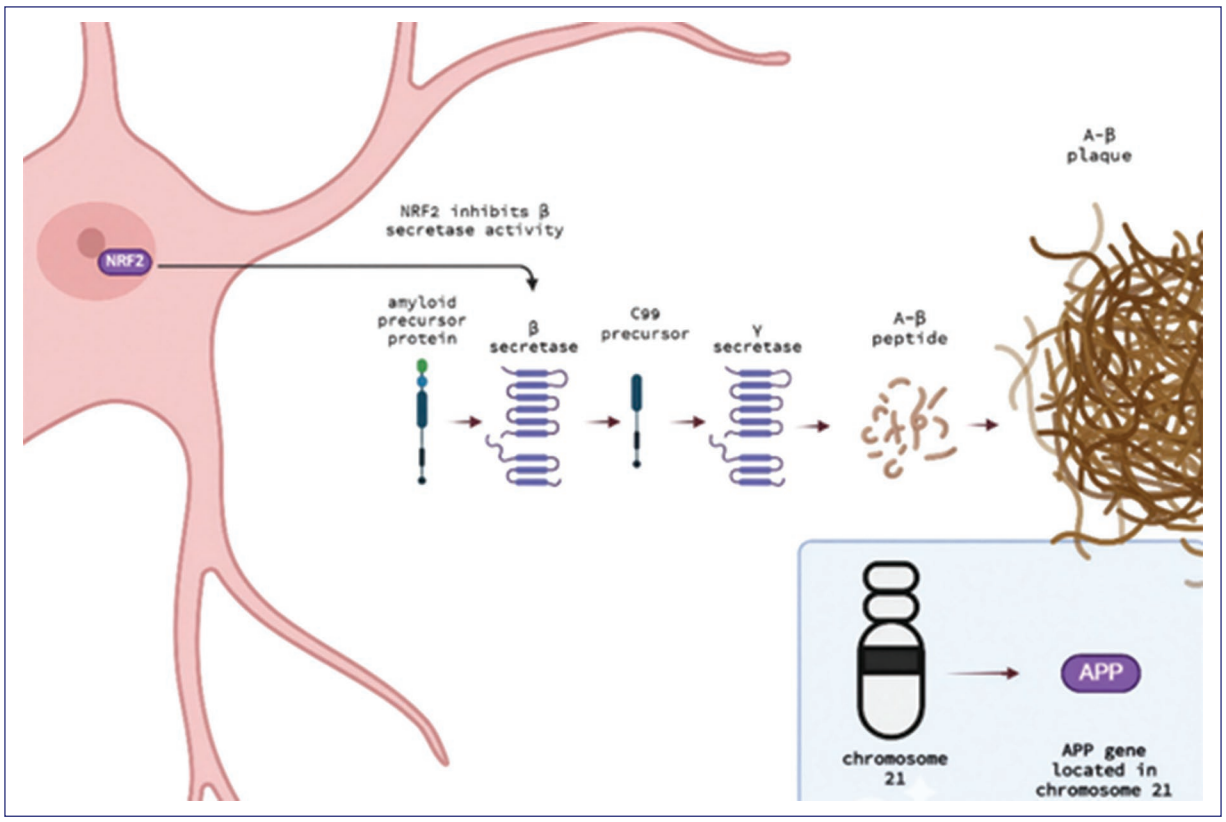


**Figure 1.** Aβ production mechanism in astrocytes. The APP undergoes an initial proteolytic cleavage by the enzyme β-secretase, generating a fragment embedded in the membrane, known as C99 due to its length of 99 amino acids. Subsequently, the enzyme γ-secretase cleaves C99 and produces the Aβ peptide. NRF2 inhibits the β-secretase activity, GPR3 promotes γ-secretase activity as well as GPR6 and 12 modulate it.

cyclase catalyzes the cyclization of an exposed glutamate at the N-terminus of Aβ, resulting in the formation of toxic pGlu-Aβ, a major component of amyloid plaques[29].

– CT1812 is a small-molecule ligand that selectively targets the component 1 subunit of the sigma2/progesterone membrane receptor. By acting as a negative allosteric modulator, it decreases the binding affinity of oligomeric Aβ, thereby mitigating the synaptic toxicity typically induced by Aβ oligomers. This mechanism presents a promising therapeutic strategy for the treatment of AD, addressing one of the key pathways involved in synaptic dysfunction[30].

## *Ligands in AD*

In AD, several ligands are implicated in the neurodegenerative process, primarily those related to proteins and neurotransmitters. Some of the key ligands include:

– Aβ: A peptide that accumulates in plaques within the brains of Alzheimer's patients.
– Tau protein: It binds to neuronal microtubules, but in AD, it becomes abnormally phosphorylated, leading to the formation of neurofibrillary tangles[31].
– N-methyl-D-aspartate receptors: These receptors are involved in excitatory synaptic transmission. Excessive activation of these receptors by glutamate can contribute to neuronal damage.
– Apolipoprotein E (ApoE4): This is a variant of the ApoE protein, which influences lipid metabolism in the brain and is associated with an increased risk of developing AD[32]. It binds to lipoprotein receptors in neurons.

The gene that encodes ApoE has three main alleles: ApoE2, ApoE3, and ApoE4, which respectively encode the different forms of apolipoprotein: ApoE-ε2, ApoE-ε3, and ApoE-ε4[33]. Each polymorphism has a different prognostic:

– APOE ε2: This is the least common allele. It reduces the risk of developing AD.
– APOE ε4: This allele is slightly more common. It increases the risk of developing AD and is associated with a more severe form of the disease.

– APOE ε3: This is the most common allele and does not appear to affect the risk of developing AD[34].

The ApoE genotyping analysis is performed to assess the genetic risk of developing AD. It can be useful in cases of a family history of the disease or in the evaluation of individuals with dementia symptoms[35].

## Glycine

Glycine is a non-essential amino acid in humans, animals, and many mammals that is synthesized from choline, serine, hydroxyproline, and threonine through interorgan metabolism[36]. Glycine, as a neurotransmitter, has the function of motor and sensory information that permits movement, vision, and audition, which is mediated by the glycine receptor (GlyR), producing inhibitory post-synaptic potentials in the CNS[37]. Glycine transporters (GlyTs) are Na+/Cl−-dependent neurotransmitter transporters responsible for glycine uptake by the CNS. GlyT1 and GlyT2 are expressed on both astrocytes and neurons, but their expression pattern in brain tissue is mainly related to neurotransmission[38]. Na+/Cl−-dependent neurotransmitter transporters known as GlyTs play a crucial role in facilitating the uptake of glycine into the CNS[4].

GlyRs are transmembrane protein complexes formed by the assembly of five subunits arranged symmetrically around a central pore, always three alphas and two betas. Five types of GlyR subunits, four alphas and one beta[39], the different combinations in these subunits make benefits in the brain, for example, alpha one/beta combination displays the fastest kinetic and has been associated with mature synapses mediating fast inhibitory neurotransmission, mainly in the spinal cord and in the brainstem[40]. Alpha two containing receptors, which display slower kinetics characterized by a slower desensitization, are abundant during development and have been found in extra-synaptic locations. Besides glycine, GlyRs can also be activated by other ligands, such as taurine and alanine[41].

## Coupled G protein receptors

G protein-coupled receptors (GPCRs) represent the largest and most diverse group of membrane receptors in eukaryotes. These cell surface receptors function as an inbox for messages in the form of light energy, peptides, lipids, sugars, and proteins. Such messages inform cells about the presence or absence of light or essential nutrients in their environment or relay information sent by other cells[42].

A GPCR consists of a long protein with three fundamental regions: an extracellular portion (the N-terminus), an intracellular portion (the C-terminus), and a middle segment containing seven transmembrane domains. Starting at the N-terminus, this long protein coils up and down through the cell membrane, with the long middle segment traversing the membrane seven times in a serpentine pattern. The last of the seven domains is connected to the C-terminus. When a GPCR binds to a ligand (a molecule with affinity for the receptor), the ligand induces a conformational change in the seven transmembrane regions of the receptor. This activation of the C-terminus subsequently recruits a substance that, in turn, activates the G protein associated with the GPCR[43]. Human GPCRs can be classified into five main families based on phylogenetic criteria: glutamate, rhodopsin, adhesion, frizzled/taste2, and Secretin[44].

The concentration of ligands, the expression of GPCR proteins, or altered mutations and signaling are implicated in various pathophysiological conditions, including CNS disorders, cardiovascular and metabolic diseases, respiratory dysfunctions, gastrointestinal disorders, immune diseases, cancer, musculoskeletal pathologies, and ocular diseases[45].

## Orphan receptors

GPCRs are called so because they carry out their actions by interacting with heterotrimeric GTPases, which in turn modulate the activity of enzymes and also some ion channels[46].

Orphan GPCRs are receptors that lack endogenous ligands. Discovered through molecular biological analyses, they served as the foundation for reverse pharmacology, a process in which efforts are made to match receptors with potential transmitters[47]. GPCRs consist of a single polypeptide that is folded with seven segments that span the entire width of the membrane and the intervening portions loop both inside and outside the cell[48]. Signal transmission inside the cells primarily occurs through the interaction of GPCRs with heterotrimeric G proteins. Heterotrimeric G proteins are made up of three different subunits (α, β, and γ), and the types of G proteins are named based on the similarity, localization, and functionality of the α subunit[49], in the role of the production of cyclic AMP, the GPCRs that stimulate the production of cyclic AMP are often coupled to the stimulatory G protein (Gs), which activates adenylate cyclase and increases cyclic AMP levels, also the GPCRs that can inhibit the synthesis of cyclic AMP by binding of an inhibitory G protein (Gi) to a GPCR[50] (Fig. 2).

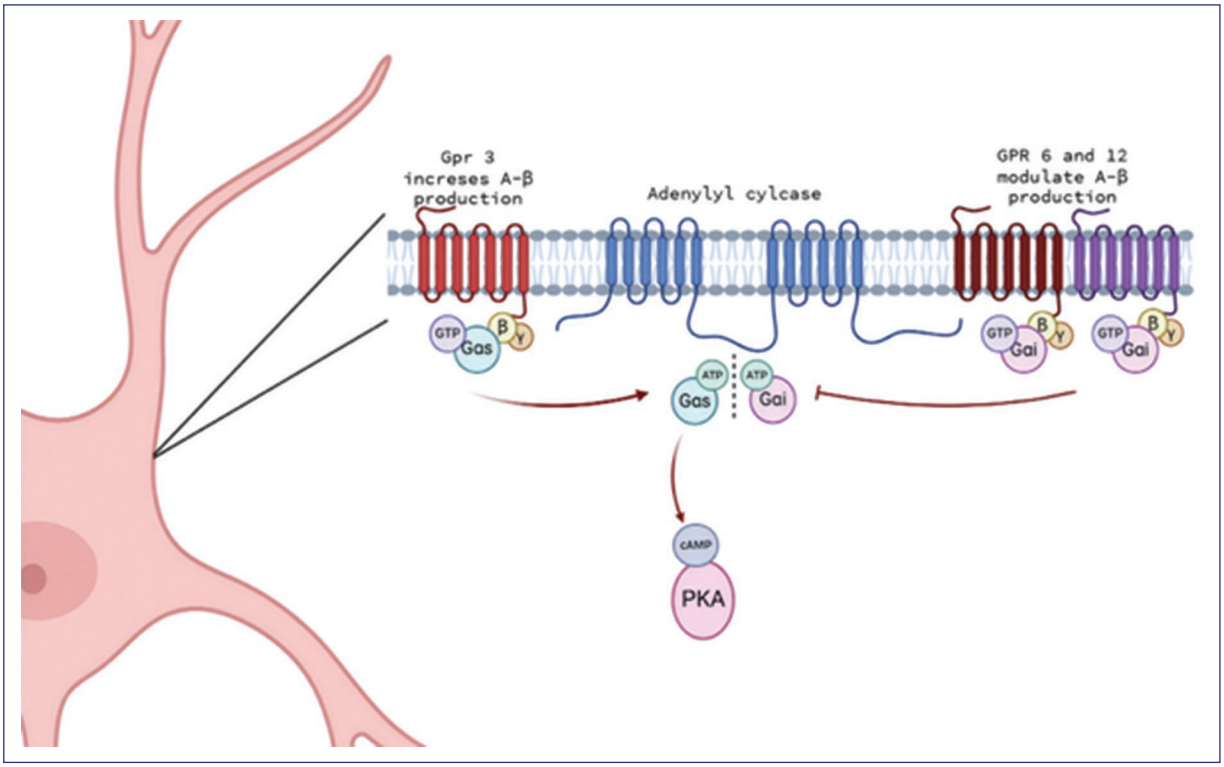


**Figure 2.** Signaling pathways mediated by GPRs. GPR3 is coupled to the Gs protein, which activates adenylyl cyclase, leading to ATP conversion into cAMP and the activation of protein kinase A. In contrast, GPR6 and GPR12 are coupled to Gi proteins, which inhibit adenylyl cyclase activity.

## *GPR3*

GPR3 is part of class A, family Gs. Class A refers to orphan receptors that have been associated with putative endogenous ligands, and Gs to the adenylyl cyclase stimulation[51].

Research has demonstrated that GPR3 modulates the generation of beta-amyloid peptides in neurons and may serve as a potential therapeutic target for the treatment of AD[52].

The expression of GPR3 mRNA is widespread among neurons in diverse brain regions, encompassing the cortex, thalamus, hypothalamus, amygdala, hippocampus, pituitary, and cerebellum[53]. It also promotes the processing of APP into the neurotoxic Aβ peptide through mechanisms that are not fully understood[52].

GPR3 exhibits constitutive activity and can signal through both G protein-dependent and independent mechanisms. Despite being classified as an orphan receptor, GPR3 shares its closest phylogenetic relation with cannabinoid receptors. Through β-arrestin2 recruitment assays, recent findings indicate that CBD acts as an inverse agonist for GPR3[53]. In pathological scenarios, GPR12 influences the response to antipsychotic drugs in individuals with schizophrenia, whereas GPR3 and GPR6 play crucial roles in neurodegenerative diseases. Pioneering studies using GPR3-deficient mouse models and histological examinations of post-mortem brains from affected patients have revealed a significant association between GPR3 and AD[54].

## *GPR6*

GPR6 is part of Class A, family Gi/Gs. Class A refers to orphan receptors that have been associated with putative endogenous ligands, Gi to the adenylyl cyclase inhibition, and Gs to the stimulation of adenylyl cyclase[55].

GPR6 is involved in instrumental learning[56]. Furthermore, the expression of GPR6 inhibited C1q-mediated neuroprotection from fAB-induced injury[57].

In addition, the regulation of complement component C1q synthesis has been documented in the brain in response to diverse forms of neuronal injury, including experimental models of AD[58].

## *GPR12*

GPR12 is part of Class A, family Gi/Gs. Class A refers to orphan receptors that have been associated

with putative endogenous ligands, Gi to the adenylyl cyclase inhibition, and Gs to the stimulation of adenylyl cyclase[59].

GPR12 promotes neurite outgrowth and blocks myelin inhibits neurite outgrowth and blocks myelin inhibition in neurons. Receptor with constitutive G(s) signaling activity that stimulates cyclic AMP production[60,61].

The inhibition of myelin-associated glycoprotein by GPR12 was linked to the inhibition of the small GTPase, RhoA, mediated by cAMP-dependent protein kinase[62].

## Discussion

Orphan GPCRs (GPR3, GPR6, and GPR12) play a key role in modulating Aβ production within AD pathogenesis. This review highlights the important role of glycine in regulating the gene expression of these GPRs, proposing a potential interaction mediated through their seven transmembrane domains as a mechanistic link. The evidence suggests that these receptors have a key role in the modulation of Aβ production.

The main studies of GPR3 provide information that it enhances γ-secretase activity, which promotes the generation of Aβ from its precursor, APP[63]. Likewise, GPR6 and GPR12 appear to modulate the γ-secretase activity, which could have some important therapeutic implications, such as the inhibition of this secretase to modulate the Aβ production by a medicament or genetic silencing[64].

The role of glycine in the GPR's modulation is another relevant aspect in this review, glycine may modulate the GPR3, GPR6, and GPR12 signaling through by its seven transmembrane domain, it is not concrete road for the activation of this receptors, but the consequence is that GPR3 is the most related to de stimulation of adenylyl cyclase levels and GPR6 and GPR12 are related to de modulation, so they can stimulate or inhibit the adenylyl cyclase levels.

Another important point to mention about glycine includes the signaling, which is determined by the activation of the GlyR. This receptor, which allows the chloride ions ($Cl^-$) to enter the cell, generates an inhibitory response in the CNS. With normal conditions, $Cl^-$ influx through GlyR hyperpolarizes the cell membrane, reducing neuronal excitability and modulating synaptic activity.

In pathological contexts such as AD, alterations in $Cl^-$ homeostasis can modify GlyR responses, contributing to abnormal neuronal excitability. This phenomenon could be involved in astrocytic dysfunction and the modulation of GPRs, which have been linked to Aβ accumulation.

Despite these promising findings, it is essential to acknowledge the study's limitations. In addition, the interaction between astrocytes, neurons, and other glial cell types requires further investigation to understand how these mechanisms integrate in AD.

## Conclusion

- The orphan GPR3, GPR6, and GPR12 are concluded to be directly and indirectly involved in regulating AD pathogenesis.
- GPR3, coupled with the Gs protein, positively promotes gamma-secretase activity, enhancing the production of Aβ peptides.
- GPR6 is linked to impaired C1q-mediated neuroprotection, whereas GPR12 promotes neurite outgrowth and counteracts myelin inhibition, indicating complex roles in neurodegeneration.
- Glycine, as an inhibitory neurotransmitter, may indirectly modulate GPR expression and activity by influencing chloride ion Cl homeostasis via its interaction with glycine transporters 1 and 2 (GlyT1/GlyT2) and GlyR in astrocytes.
- Disrupted $Cl^-$ homeostasis in AD likely contributes to astrocytic dysfunction and abnormal neuronal activity, thereby exacerbating beta accumulation and neurodegeneration.

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## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Ethical considerations

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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