Advances in Oral and Maxillofacial Surgery 23 (2026) 100683

Contents lists available at ScienceDirect

Advances in Oral and Maxillofacial Surgery

journal homepage: www.sciencedirect.com/journal/advances-in-oral-and-maxillofacial-surgery

Full Length Article

Evaluation of the effectiveness of a nanotechnological device (Taopatch®) in the management of temporomandibular disorders in pediatric and adult patients: a controlled clinical study

Vesela Stoichkova [a,*,1], Gianna Dipalma [b,c,1], Giuseppe Messina [d,**], Lorenzo Silenzi Ederli [e], Francesca Russo [f], Elisabetta Guercio Monaco [g], Laura Ferrante [c], Francesco Inchingolo [c], Vito Crincoli [c], Angelo Michele Inchingolo [c], Andrea Palermo [h], Alessio Danilo Inchingolo [c,2], Sabina Saccomano [b,2]

[a] Department of Orthodontics, Faculty of Dental Medicine, Medical University-Sofia, Bulgaria
[b] Department of Life Science, Health, and Health Professions - Link Campus University Italy, Macerata, Italy
[c] Department of Interdisciplinary Medicine, University of Bari "Aldo Moro", Bari, 70121, Italy
[d] Department of Human Sciences and Promotion, Quality of Life San Raffaele University, Rome, Italy
[e] Department of Health, Life and Environmental Science, University of L'Aquila, Piazza Salvatore Tommasi, Italy
[f] Private Practitioner, Italy
[g] Universidad Central de Venezuela, Universidad Alfonso X el Sabio, Madrid, Spain
[h] Department Experimental of Medicine, University of Salento, Lecce, 73100, Italy

ARTICLE INFO

Keywords:
Pain relief
TMJ
Maximum opening
Nanotechnology
Taopatch®
Placebo

ABSTRACT

Aim of the study: The aim of study is to evaluate the effect of Taopatch® and their influence on the patient's comfort as maximum opening of the mouth and pain. Temporomandibular joint (TMJ) dysfunction affects a significant portion of the population and can lead to pain and functional limitations, impacting quality of life. The etiology is multifactorial, requiring multifaceted therapeutic approaches. Nanotechnology, such as the Taopatch® device, offers promising support in pain relief and function improvement. This study evaluates the effect of Taopatch® on mouth opening and TMJ pain relief in both adults and children.

Material and method: One hundred forty-nine patients (73 adults and 76 children) have been examined before (pre) and after (post) the application of Taopatch® type TMJ A placebo group of 43 patients have been examined according to the same parameters.

Conclusion: The biophotons of TMJ Taopatch® can be useful in the daily practice of dentists, to increase the amount of maximum mouth opening and pain control.

1. Introduction

Facial pain is a complex and heterogeneous symptom, which can originate from multiple causes, ranging from odontogenic and musculoskeletal disorders to neurological, inflammatory, and even psychosomatic conditions [1–3].

Its prevalence in the general population is significant, and it represents one of the most frequent complaints encountered in both dental and medical practice [4–7]. Facial pain can affect individuals of any age, from children to the elderly, and the therapeutic approach must necessarily be tailored to the underlying etiology [8–16].

Among the most common causes of facial pain, there are disorders

* Corresponding author.
** Corresponding author.
E-mail addresses: v.stoichkova@fdm.mu-sofia.bg (V. Stoichkova), g.dipalma@unilink.it, gianna.dipalma@uniba.it (G. Dipalma), giuseppe.messina@uniroma5.it (G. Messina), lorenzo.silenziederli@student.univaq.it (L.S. Ederli), francescarrusso1999@gmail.com (F. Russo), elizabetta.guercio@ucv.ve (E.G. Monaco), lauraferrante79@virgilio.it (L. Ferrante), francesco.inchingolo@uniba.it (F. Inchingolo), vito.crincoli@uniba.it (V. Crincoli), angelomichele.inchingolo@uniba.it (A.M. Inchingolo), andrea.palermo@unisalento.it (A. Palermo), alessiodanilo.inchingolo@uniba.it (A.D. Inchingolo), s.saccomanno@unilink.it (S. Saccomano).
[1] These authors contributed equally to this work as co-first authors.
[2] These authors contributed equally to this work as co-last authors.

https://doi.org/10.1016/j.adoms.2026.100683
Received 12 May 2026; Accepted 15 May 2026
Available online 19 May 2026

involving the temporomandibular joint (TMJ) and the associated masticatory muscles [17–26].

Temporomandibular disorders (TMDs) are in fact recognized as a major contributor to orofacial pain, with a prevalence estimated between 5% and 12% of the population, though some studies report higher percentages depending on the diagnostic criteria adopted [27–33].

Epidemiological evidence also indicates a marked gender difference, with women being affected more frequently than men, particularly in the age range between 20 and 40 years, possibly due to hormonal, anatomical, and psychosocial factors [34–38].

Temporomandibular pain is a multifactorial condition, where both structural and functional alterations may coexist. Its pathophysiology is influenced by occlusal discrepancies, parafunctional habits such as bruxism, postural imbalances, muscle hyperactivity, stress, and systemic factors including hormonal variations and genetic predisposition [39–47]. For this reason, the therapeutic approach must not only be aimed at symptom control, but also at identifying and correcting the underlying causes to prevent chronicity and recurrence.

The treatment of TMD pain is therefore highly variable and depends on the severity of the symptoms, the duration of the disorder, and the degree of functional limitation. Current strategies include pharmacological therapy (analgesics, muscle relaxants, anti-inflammatories), physiotherapy and manual therapy, occlusal appliances such as stabilization splints, and, in selected cases, minimally invasive or surgical interventions [48–54].

Despite the heterogeneity of available treatments, it is widely recognized that pain and limitations in mandibular opening can be extremely debilitating, with a significant impact on the patient's daily life, interfering with essential activities such as chewing, swallowing, speaking, and even social interaction, thus compromising overall quality of life [55–65].

The limitation of mouth opening, often referred to as trismus, together with the associated pain, may derive from different factors including temporomandibular dysfunction, intra-articular inflammation, dental pathologies, muscle disorders, and myofascial pain syndromes [66–71].

Once the etiology has been properly identified, the therapeutic pathway must be oriented towards the most appropriate treatment, with the dual objective of pain relief and functional recovery [72–76].

In recent years, scientific research has shown growing interest in the application of nanotechnology and photobiomodulation as supportive tools in the management of musculoskeletal and orofacial pain. Although the current body of evidence is still limited, and further large-scale studies are required, preliminary data suggest that nanotechnological devices capable of emitting light at specific therapeutic wavelengths may promote cellular bioactivation, enhance tissue oxygenation, and modulate nociceptive responses [77–84].

Among these devices, the Taopatch® has attracted attention as an innovative non-invasive approach.

By exploiting nanotechnology, the device emits therapeutic light wavelengths activated by body heat, with the potential to reduce pain and improve functional mobility. Initial clinical applications suggest that Taopatch® may be useful as a complementary tool in the management of various pain disorders, including those related to the temporomandibular joint [85–92].

The aim of this study is therefore to investigate, within the context of daily orthodontic and dental practice, the potential effects of the Taopatch® device on patients affected by temporomandibular dysfunction. Specifically, the study evaluates its impact on two key parameters: (1) the maximum mouth opening, a fundamental indicator of mandibular function, and (2) the degree of pain relief in the area of the temporomandibular joint and selected masticatory muscles [93–96].

The investigation was conducted on both adult and pediatric populations, in order to highlight possible age-related differences and to broaden the clinical perspectives of this technology [97–108].

1.1. Treatment procedure

The Taopatch® is an innovative nanotechnological medical device, designed in the form of a thin, circular microchip with a diameter of approximately 16 mm and a thickness of less than 1 mm.

The device is applied directly to the patient's skin through the use of a small adhesive patch, which ensures stability and comfort during treatment.

Once positioned, it remains in situ for the entire duration of therapy, without interfering with daily activities and without causing discomfort to the patient.

The external coating of the patch is made of Mylar®, a lightweight, hypoallergenic, and biocompatible material widely used in biomedical applications.

This coating has the dual function of protecting the internal nanostructures and ensuring complete safety and tolerance on the skin, minimizing the risk of irritation or allergic reactions.

The device incorporates quantum dots, nanocrystals capable of interacting with light and electromagnetic radiation. These nanostructures are known to exhibit specific optical properties in experimental settings. However, the application of quantum dot technology in this specific device and its clinical effects are still under investigation, and current evidence is limited. Therefore, the proposed mechanism of action should be considered as based on preliminary and theoretical evidence.

1.2. Mechanism of action

The Taopatch® device is proposed to work through a mechanism consistent with the principles of photobiomodulation. The device is designed to emit low-intensity electromagnetic radiation in the red and near-infrared (NIR) spectrum, which is activated by body heat [109–114].

These wavelengths are known to penetrate biological tissues and interact with cellular components, particularly at the mitochondrial level. One of the primary targets is cytochrome *c* oxidase (CCO), a key enzyme in the mitochondrial respiratory chain. The interaction between light and CCO is believed to facilitate the dissociation of nitric oxide (NO), thereby restoring enzyme activity and enhancing oxidative phosphorylation.

As a consequence, there is an increase in adenosine triphosphate (ATP) production, which may improve cellular metabolism and promote tissue recovery. In addition, photobiomodulation has been associated with modulation of inflammatory mediators, reduction of oxidative stress, and alteration of nociceptive signaling pathways.

In the context of TMD, these effects may contribute to the reduction of pain and improvement of muscular function, particularly in the masticatory system. Although the exact biological mechanisms underlying the effects of Taopatch® require further investigation, its action can be reasonably interpreted within the framework of light-based therapeutic modulation [115].

2. Materials and methods

The present study was designed to evaluate the clinical efficacy of the Taopatch® TMJ nanotechnological device in dental and orthodontic practice.

The investigation focused primarily on two functional and symptomatic parameters: (1) the maximum mouth opening (measured in millimeters), and (2) the pain response of the lateral pterygoid muscle during intraoral palpation.

These measurements were performed under three distinct experimental conditions: without any applicator, with a placebo applicator, and with the active Taopatch® device.

In addition to these parameters, the study also assessed the level of perceived stress in both children and adults.

This was motivated by preliminary observations suggesting that stress might influence the subjective experience of pain and the functional adaptation of the stomatognathic system.

To ensure scientific rigor, the study included a placebo control group, composed of both children and adults, in order to distinguish the specific effects of Taopatch® from potential placebo responses. In this group, participants were subjected to identical procedures, except that a simple adhesive tape without the applicator was applied in front of the tragus, simulating the positioning of the real device.

The tape used was the same as that employed to secure the active Taopatch® in the experimental group. The absence of significant changes in this group reinforced the validity of the results observed in the active treatment groups, highlighting the intrinsic therapeutic efficacy of Taopatch®.

2.1. Study population

The study was not randomized; participants were consecutively allocated to groups. A total of 149 patients were enrolled and examined before (pre) and after (post) the application of the Taopatch® TMJ device (Fig. 1).

The sample included:

The sample represents a convenience sample derived from clinical practice and no prior power calculation was performed.

Adults: 73 participants, mean age 33.52 ± 9.37 years, with a gender distribution of 27.4% male and 72.6% female.

Children: 76 participants, mean age 10.62 ± 2.49 years, with 60.5% male and 39.5% female.

The placebo group consisted of 43 individuals (mean age 23.44 ± 9.42 years, range 7–53). Within this subgroup, 34.9% were male and 65.1% were female, with children representing 18% of the total. The smaller size and wider age range of the placebo group were due to recruitment constraints during the study period.

Diagnosis was based on DC/TMD criteria. No formal sample size calculation was performed. The sample size was determined based on the number of eligible patients available during the study period.

2.2. Pain and functional measurements

Pain intensity was quantified using the 0–10 Visual Analog Scale (VAS), where 0 indicated the absence of pain and 10 the maximum level of pain imaginable. VAS was used exclusively to quantify pain intensity and not for diagnostic classification of TMD. The VAS scale was selected due to its simplicity and widespread use in clinical pain assessment. However, in pediatric patients, its reliability may be influenced by age-related cognitive and interpretative variability.

Palpation was directed to the temporal tendon insertion on the medial aspect of the coronoid process, bilaterally, and was consistently performed by the same trained operator to minimize variability. Although the pressure applied during palpation was not instrumentally calibrated, efforts were made to maintain a consistent and reproducible technique across all participants.

The intraoral palpation technique involved inserting the index finger behind the upper last molars, applying upward and inward pressure in a direction lateral to the maxillary tuberosity and medial to the coronoid process (Fig. 2).

This specific area was chosen because the lateral pterygoid muscle, despite being relatively small, is considered one of the primary muscles implicated in temporomandibular joint disturbances and thus plays a key role in pain generation.

The maximum mouth opening was measured using a calibrated Dentaurum® sliding caliper, expressed in millimeters (Fig. 3).

For each participant, three separate measurements were taken for the following parameters:

1. Maximum mouth opening.
2. Pain intensity on the right side during palpation.
3. Pain intensity on the left side during palpation.

These measurements were repeated both before and immediately after the application of the Taopatch® device (Fig. 4).

Participants were evaluated under baseline conditions without ongoing specific TMD treatment, and the intervention was applied as a single-session complementary approach.

2.3. Device application protocol

For the experimental group, the Taopatch® TMJ applicators were placed bilaterally in front of the tragus. Following the application, each patient was instructed to drink a glass of water (approximately 150 ml at room temperature) and then to walk 50 steps while moving the head, shoulders, and entire body energetically.

This standardized routine was intended to stimulate neuromuscular activation and ensure consistent baseline conditions across all

Fig. 1. Application of a Taopatch® TMJ a) in a child and b) in an adult.

Fig. 2. Palpation with applied Taopatch® TMJ a) for a child and b) for an adult.

Fig. 3. Measurement of the maximum mouth opening with a metal ruler a) in a child and b) in an adult.

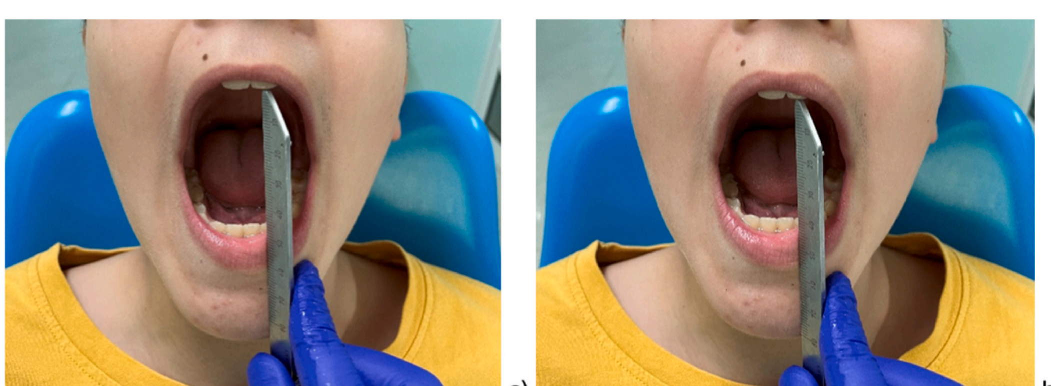

Fig. 4. The maximum mouth opening improves a) without Taopatch® TMJ and b) with Taopatch® TMJ.

participants.

The outcome measurements were collected immediately after the walking task, corresponding to approximately 3 min after application of the Taopatch®, rapid onset photobiomodulation effects.

This timeframe was selected because preliminary clinical evidence suggested that the device could produce immediate effects, comparable to the onset of common analgesics.

2.4. Stress assessment

The level of lifestyle-related stress was assessed using the same 0–10 VAS scale (0 = no stress, 10 = maximum stress). Participants in both groups, children and adults, were asked to rate their subjective stress level during the evaluation session.

This parameter was included to explore potential correlations between stress, pain perception, and the functional impact of Taopatch®. Stress was assessed using a single-item VAS scale, reflecting subjective perceived stress rather than a validated psychometric instrument.

2.5. Operator consistency

The study was conducted without blinding. To minimize inter-operator variability, all palpations, measurements, and stress assessments were conducted by the same trained investigator.

This methodological choice was essential to reduce bias and ensure that differences in applied pressure or technique did not influence the outcomes. However, it should be noted that the lack of instrumental calibration of palpation pressure represents a methodological limitation of the study.

2.6. Statistical analysis

No formal sample size calculation was performed. The sample size was determined based on the number of eligible patients available during the study period. The statistical analysis included descriptive statistic, frequency analysis, the Independent Samples Test, the Paired samples Statistics and T-test. (Tables 1–4 and Figs. 5 and 6).

The Independent Samples Test, Levene's Test for Equality of Variances, was used to find out statistically significant differences between the two groups of adults and children $t(148) = 8.890$, $p = .000$. These tests were selected due to the exploratory nature of the study and the focus on pre–post comparisons. However, no multivariate analysis was performed, which may represent a limitation in fully assessing the influence of potential confounding variables. Confidence intervals (95% CI) were calculated and reported to provide an estimate of the precision of the observed effects.

2.7. Inclusion and exclusion criteria

Participants were recruited from patients attending the dental and orthodontic clinic presenting with signs and symptoms consistent with temporomandibular disorders (TMD).

Inclusion criteria were:

- presence of pain in the temporomandibular joint and/or masticatory muscles;
- limitation or discomfort during mouth opening or mandibular function;
- age compatible with the study groups (children and adults);
- ability to understand and respond to the Visual Analog Scale (VAS).

Exclusion criteria included:

- history of recent trauma affecting the temporomandibular joint;
- ongoing pharmacological treatment for TMD or chronic pain conditions;
- presence of systemic diseases potentially influencing pain perception (e.g., neurological or rheumatologic disorders);
- previous surgical interventions involving the TMJ;
- inability to comply with the study procedures.

The diagnosis of TMD was based on clinical evaluation of symptoms and functional signs, including pain during mandibular movement or muscle palpation and limitation of mouth opening. However, standardized diagnostic criteria such as DC/TMD were not formally applied.

The VAS scale was used exclusively to quantify pain intensity and was not considered a diagnostic tool.

3. Results

1. All measured parameters have shown improvement after the application of the human upgrade device Taopatch® TMJ in all patients.
2. Both adults and children reacted positively to the therapy and the results were immediate.
3. In the group of adults the max opening has increased from 48.36 ± 6.715 mm to 51.43 ± 6.463 mm ($t(72) = 11.255$, $p = .000$). The pain on the right side during palpation has reduced from 4.89 ± 2.547 to 3.15 ± 2.301. Statistically significant differences were found in the group of adults before and after the application of the nanotechnology $t(72) = 10.813$, $p = .000$ for the right side and $t(72) = 9.728$, $p = .000$ for the left side. (pic.4)
4. In the group of children the max opening has increased from 45.48 ± 6.871 mm to 48.45 ± 6.867 mm ($t(75) = 13.838$, $p = .000$). The pain on the right side during palpation has reduced from 5.70 ± 2.683 to 3.74 ± 2.479. The pain on the left side has reduced from 6.38 ± 2.612 to 4.24 ± 2.427. Statistically significant differences were found in the group of children before and after the application of the nanotechnology $t(75) = 8.993$, $p = .000$ for the right side and $t(75) = 9.421$, $p = .000$ for the left side.
5. The level of stress in adults was high 6.74 ± 2.17, while in children the stress was half less 3.30 ± 2.53. In the placebo group the level of stress was 6.33 ± 2.201.
6. No statistically significant changes have been found in the placebo group in the maximum mouth opening before (pre) and after (post) the application of the placebo tape ($t(42) = 0.682$, $p = .499$).
7. No statistically significant changes have been found in the placebo group in the pain during palpation from the right or from the left side before (pre) and after (post) the application of the placebo tape. (right side $t(42) = 1.756$, $p = .086$; left side $t(42) = 0.846$, $p = .403$).

Interestingly, during the initial evaluation, adult participants reported approximately twice the stress levels compared to children. Conversely, children exhibited higher pain responses during palpation

Table 1
Results before (pre) applying Taopatch® TMJ and after (post) its application in adults (with 95% CI).

Parameter	Pre (Mean ± SD)	Post (Mean ± SD)	t (df = 72)	p-value	95% CI (Pre)	95% CI (Post)
Maximum Opening	48.36 ± 6.715	51.43 ± 6.463	11.255	<0.001	46.82 – 49.90	49.94 – 52.92
Pain Right (R)	4.89 ± 2.547	3.15 ± 2.301	10.813	<0.001	4.31 – 5.47	2.62 – 3.68
Pain Left (L)	4.89 ± 2.325	3.32 ± 2.185	9.728	<0.001	4.36 – 5.42	2.82 – 3.82

95% confidence intervals (CI) were calculated for pre- and post-treatment mean values.

Table 2
Results before (pre) applying Taopatch TMJ and after (post) its application in children (with 95% CI).

Parameter	Pre (Mean ± SD)	Post (Mean ± SD)	t (df = 75)	p-value	95% CI (Pre)	95% CI (Post)
Maximum Opening	45.48 ± 6.871	48.45 ± 6.867	13.838	<0.001	43.94 – 47.02	46.91 – 49.99
Pain Right (R)	5.70 ± 2.683	3.74 ± 2.479	8.993	<0.001	5.10 – 6.30	3.18 – 4.30
Pain Left (L)	6.38 ± 2.612	4.24 ± 2.427	9.421	<0.001	5.79 – 6.97	3.70 – 4.78

95% confidence intervals (CI) were calculated for pre- and post-treatment mean values.

Table 3
Paired Samples *t*-test for the placebo group – maximum mouth opening before and after the application of the placebo tape (with 95% CI).

Parameter	Pre (Mean ± SD)	Post (Mean ± SD)	t (df = 42)	p-value	95% CI (Pre)	95% CI (Post)
Maximum Opening	48.42 ± 6.165	48.17 ± 5.928	0.682	0.499	46.58 – 50.26	46.40 – 49.94

95% confidence intervals (CI) were calculated for pre- and post-treatment mean values.

Table 4
Paired Samples *t*-test for the placebo group - pain during palpation before and after the application of the placebo tape (with 95% CI).

Parameter	Pre (Mean ± SD)	Post (Mean ± SD)	t (df = 42)	p-value	95% CI (Pre)	95% CI (Post)
Pain Right (R)	6.02 ± 2.464	5.79 ± 2.465	1.756	0.086	5.28 – 6.76	5.05 – 6.53
Pain Left (L)	5.93 ± 2.404	5.79 ± 2.366	0.846	0.403	5.21 – 6.65	5.08 – 6.50

95% confidence intervals (CI) were calculated for pre- and post-treatment mean values.
No statistically significant differences were observed in the placebo group for pain during palpation, either on the right side (p = .086) or on the left side (p = .403).

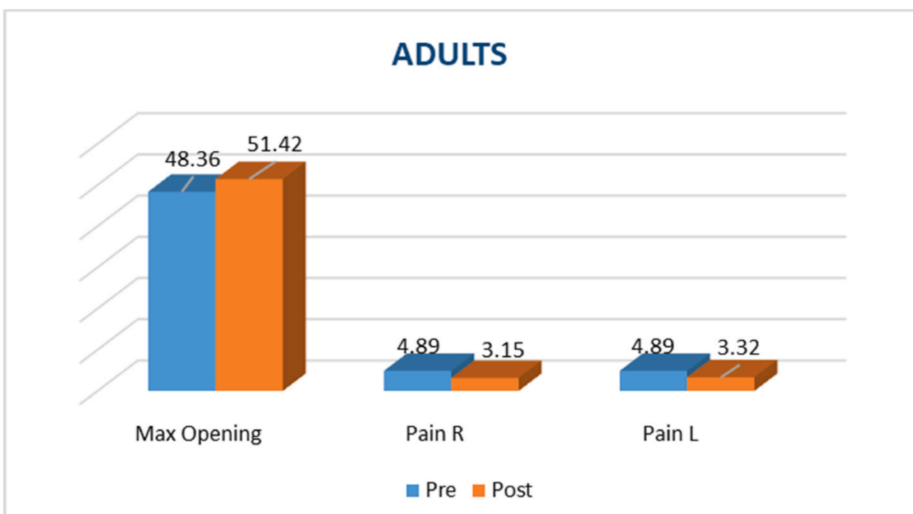

Fig. 5. Improvement in the mouth opening and pain relief with Taopatch® TMJ in adults.

in the absence of any patch, a result that could be attributed to several factors.

On one hand, children may demonstrate greater sensitivity to tactile stimuli or increased tenderness of the tissues. On the other hand, the challenge of accurately quantifying pain on a 0-to-10 visual analog scale (VAS) could also contribute to this observation.

Notably, despite some initial hesitation in responding, most children were able to determine their stress levels with relative accuracy using the same VAS system.

4. Discussion

The use of intraoral palpation targeting the lateral pterygoid region represents a methodological limitation, as this muscle is difficult to assess reliably and may be influenced by adjacent anatomical structures, such as the temporalis tendon. This may reduce the specificity of pain assessment. The biological mechanisms underlying the effects of the device, particularly those related to quantum dot technology, remain not fully elucidated and should be interpreted with caution. Pain and functional limitation represent two of the most disabling manifestations of temporomandibular disorders (TMD), as they directly interfere with essential daily functions such as mastication, phonation, swallowing, and even social interaction.

Patients suffering from TMD often experience a significant reduction in quality of life, not only due to chronic orofacial pain but also because of the psychological burden associated with functional impairment, which may lead to stress, anxiety, and social withdrawal [116–123]. In this clinical context, the search for non-invasive and safe therapeutic solutions has become a priority. Among the various conservative treatment strategies available, the use of nanotechnological devices such as Taopatch® emerges as a promising complementary option, capable of integrating with established protocols such as physiotherapy, occlusal splints, and behavioral interventions [124–129]. The rationale for this combined approach lies in the multimodal nature of TMD, where structural, muscular, and psychosocial components coexist and require a holistic management strategy [130–135]. The results obtained in this

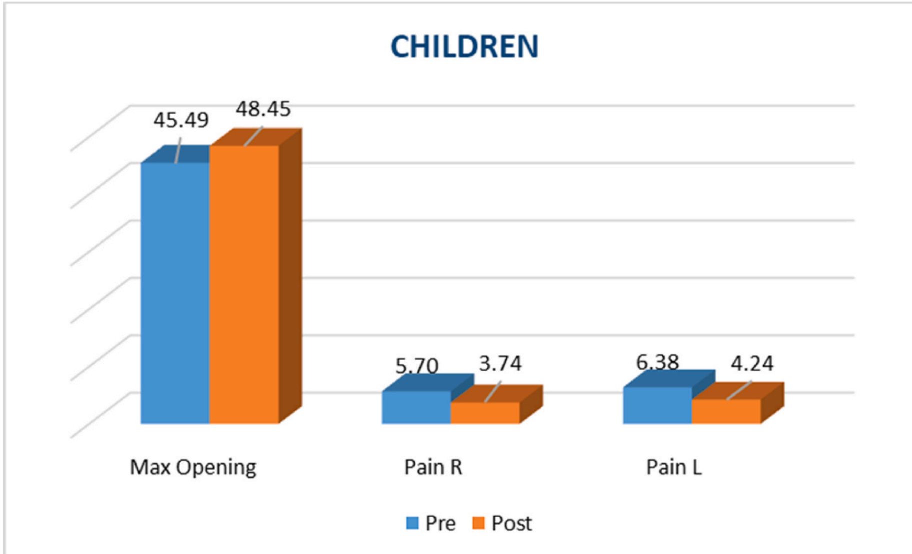

Fig. 6. Improvement in the mouth opening and pain relief with Taopatch® TMJ in children.

study provide encouraging evidence. The application of the Taopatch® TMJ device produced immediate and statistically significant improvements in both maximum mouth opening and pain reduction during palpation of the lateral pterygoid muscle [136–145]. These results were consistent across both adult and pediatric groups, although children exhibited particularly favorable responses, possibly due to greater tissue plasticity, higher responsiveness of the neuromuscular system, or differences in pain perception thresholds. It should be noted that the use of the VAS scale in children may present limitations, as younger patients may have difficulty accurately interpreting and quantifying pain levels. This aspect could have influenced the reported pain scores. The comparison with the placebo group is especially relevant: the absence of significant improvements in participants treated with simple adhesive tape reinforces the hypothesis that the effects observed are attributable to the specific photobiomodulatory action of the Taopatch®, rather than to psychosomatic or contextual factors. Moreover, the absence of reported adverse events underscores the safety profile of the device, confirming its suitability for use in diverse populations, including pediatric patients and individuals seeking non-pharmacological alternatives. Nevertheless, while these findings are encouraging, they must be interpreted with caution. The scientific literature regarding light-emitting nanotechnological devices for TMD management is still in its early stages [146–153].

Although preliminary results are promising, there is an urgent need for larger, multicenter randomized controlled trials (RCTs) with longer follow-up periods. Such studies would allow for the confirmation of the present outcomes, the assessment of long-term stability of results, and the exploration of additional clinical benefits, such as improved muscular coordination, reduction of parafunctional habits, or enhanced postural balance [154–165].

Another intriguing aspect is the potential extension of Taopatch® applications beyond TMD treatment. Emerging evidence suggests that nanophotonic stimulation may play a role in the regulation of sleep quality, a domain of growing clinical and social relevance.

Sleep disorders are increasingly prevalent worldwide and are associated with reduced cognitive performance, impaired emotional regulation, and increased risk of systemic diseases [166–173].

Non-pharmacological solutions, by virtue of their safety and non-invasiveness, are gaining popularity, as they avoid the side effects and dependency risks associated with pharmacological therapies [174–179].

In this regard, the development of the Repose Tao pillow, which integrates Taopatch® technology into an ergonomic cervical support, represents an innovative attempt to transfer photobiomodulation into the domain of sleep medicine [180,181].

In a recent pilot study involving 30 participants, the pillow was used nightly over a four-week period, with sleep quality assessed through the Pittsburgh Sleep Quality Index (PSQI) [97,182–186].

The results indicated significant improvements in several parameters: reduced sleep latency, increased perceived sleep duration, and overall better subjective sleep quality. These findings suggest that Taopatch® technology, when embedded in ergonomic devices, could represent a valid non-invasive aid for managing insomnia and related disorders. The integration of such advanced technologies into everyday clinical practice highlights a broader perspective: nanotechnology-assisted devices could become a valuable bridge between conventional medicine and innovative, patient-centered therapeutic strategies. Their versatility, safety, and immediate clinical impact make them not only suitable for TMD management, but also promising tools in other domains of rehabilitation and preventive medicine. The imbalance between the experimental and placebo groups, particularly in terms of sample size and age distribution, represents a limitation that may affect the comparability of the results. Although the increase in maximum mouth opening was approximately 3 mm, this improvement may be clinically relevant in patients with functional limitation, as even small changes can positively impact mastication, speech, and overall quality of life.

4.1. Limitations of the study

The lack of standardized diagnostic criteria (e.g., DC/TMD) and the use of a less reliable anatomical site for pain assessment may have influenced the validity of the results. Despite the promising results, several limitations should be considered when interpreting the findings of this study. First, the study was not randomized, and participants were recruited as a convenience sample from clinical practice. Moreover, no a priori sample size calculation was performed, which may limit the statistical power and generalizability of the results. Second, the evaluation focused exclusively on the immediate, short-term effects following the application of the Taopatch® device. Consequently, no conclusions can be drawn regarding the long-term efficacy or stability of the observed improvements. Third, although a placebo group was included, the study did not adopt a double-blind design. This may have introduced potential bias related to both patient expectations and operator awareness. In addition, pain and stress were assessed using subjective measures based on the Visual Analog Scale (VAS). While widely used in clinical research, this tool may be influenced by individual perception and variability, particularly in pediatric patients, where cognitive and interpretative factors may affect reliability. Furthermore, the diagnosis of temporomandibular disorders was based on clinical evaluation without the use of standardized diagnostic protocols, such as the DC/TMD criteria. Patients were included based on the presence of TMD-related symptoms, without differentiation between muscular, articular, or mixed subtypes, which may affect the reproducibility and specificity of the findings. Finally, the imbalance between the experimental and placebo groups, particularly in terms of sample size and age distribution, represents an additional limitation that may influence the comparability of the results. Future research should address these limitations by adopting randomized controlled designs, larger and adequately powered samples, standardized diagnostic criteria, and long-term follow-up assessments to better define the clinical effectiveness of the device.

5. Conclusion

Within the limitations of this study, the application of the Taopatch® TMJ device was associated with a statistically significant immediate improvement in maximum mouth opening and a reduction in pain during muscle palpation in both adult and pediatric patients with temporomandibular disorders.

No significant changes were observed in the placebo group, suggesting that the observed effects may be related to the active device.

These findings support the potential role of Taopatch® as a non-invasive adjunctive tool in the management of TMD. However, further randomized controlled trials with larger samples and long-term follow-up are required to confirm these results and better define its clinical applications.

Informed consent statement

Informed consent was obtained from all subjects involved in the study. For minors, informed consent was obtained from parents or legal guardians.

Author contributions

Conceptualization, S.S., A.M.I. and A.D.I.; methodology, A.D.I.; software, A.M.I.; validation, F.I.; formal analysis, S.S.; investigation, V. S.; resources, L.F., G.D. and A.D.I.; data curation, V.C. and L.S.E. group; writing—original draft preparation, S.S., G.D., V.S., G.M., L.S.E., A.P., L. F. and A.M.I.; writing—review and editing, A.D.I., F.I., V.C., E.G.M. and F.R.; visualization, A.P. L.F. and F.R.; supervision, F.I.; project administration, G.D.; funding, G.M. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki (revised 2000, Edinburgh), and approved by the Ethics Committee IRCCS of Istituto Oncologico "Gabriella Serio" University of Medicine and Farmacy (Prot. 1980/CEL).

Funding

The present study was supported by a grant from the Ministry of Research, Innovation and Digitization, CNCS—UEFISCDI, project number PN-III-P4-PCE-2021-1140, within PNCDI III, a financial support for which the authors are thankful. Project -" Innovative Technological Approaches for validation of Salivary AGEs as novel biomarkers in evaluation of risk factors in diet-related diseases" SALIVAGES number. 25/1.09.2017.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The present study was supported by a grant from the Ministry of Research, Innovation and Digitization, CNCS—UEFISCDI, project number PN-III-P4-PCE-2021-1140, within PNCDI III, a financial support for which the authors are thankful. Project -" Innovative Technological Approaches for validation of Salivary AGEs as novel biomarkers in evaluation of risk factors in diet-related diseases" SALIVAGES number. 25/1.09.2017.

Abbreviations

The following abbreviations are used in this manuscript:

ATP	Adenosine Triphosphate
CCO	Cytochrome *c* Oxidase
NIR	Near-Infrared
NO	Nitric Oxide
PSQI	Pittsburgh Sleep Quality Index
RCTs	Randomized Controlled Trials
TMD	Temporomandibular Disorder
TMDs	Temporomandibular Disorders
TMJ	Temporomandibular Joint
VAS	Visual Analog Scale

References

[1] Zakrzewska JM. Differential diagnosis of facial pain and guidelines for management. Br J Anaesth 2013;111:95–104. https://doi.org/10.1093/bja/aet125.

[2] Crincoli V, Inchingolo AD, Marinelli G, Lagioia R, Bassi P, Ciocia C, Calò F, Deodato R, Marsella G, Inchingolo F, et al. Evaluation of the possible correlation between dental occlusion and craniomandibular disorders by means of teethan® electromyography: clinical-observational study on 20 patients. J Clin Med 2025; 14:5508. https://doi.org/10.3390/jcm14155508.

[3] Grassia V, Fiori A, Diodati F, Sayahpour B, Jamilian A, Armogida NG, d'Apuzzo F, Nucci L. Clear aligners: a network and bibliometric analysis of 50 pivotal articles. Dent Med Probl 2025;62:161–71. https://doi.org/10.17219/dmp/188319.

[4] Scoppa F, Saccomanno S, Bianco G, Pirino A. Tongue posture, tongue movements, swallowing, and cerebral areas activation: a functional magnetic resonance imaging study. Appl Sci 2020;10:6027. https://doi.org/10.3390/app10176027.

[5] Verrill PJ. Pain control in dentistry. Br Dent J 1980;149:362–3. https://doi.org/10.1038/sj.bdj.4804524.

[6] Malcangi G, Patano A, Pezzolla C, Riccaldo L, Mancini A, Di Pede C, Inchingolo AD, Inchingolo F, Bordea IR, Dipalma G, et al. Bruxism and botulinum injection: challenges and insights. J Clin Med 2023;12:4586. https://doi.org/10.3390/jcm12144586.

[7] Al-Wayli H. Treatment of chronic pain associated with nocturnal bruxism with botulinum toxin. A prospective and randomized clinical study. J Clin Exp Dent 2017;9:e112–7. https://doi.org/10.4317/jced.53084.

[8] Valesan LF, Da-Cas CD, Réus JC, Denardin ACS, Garanhani RR, Bonotto D, Januzzi E, de Souza BDM. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. Clin Oral Invest 2021;25:441–53. https://doi.org/10.1007/s00784-020-03710-w.

[9] Silva MAG, Pantoja LLQ, Dutra-Horstmann KL, Valladares-Neto J, Wolff FL, Porporatti AL, Guerra ENS, De Luca Canto G. Prevalence of degenerative disease in temporomandibular disorder patients with disc displacement: a systematic review and meta-analysis. J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg 2020;48:942–55. https://doi.org/10.1016/j.jcms.2020.08.004.

[10] Balel Y, Yildiz S, Gokce E, Tumer MK, Ege B. Does temporomandibular joint magnetic resonance imaging diagnosis support clinical examination diagnosis following diagnostic criteria for temporomandibular disorders? J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg 2023;81:813–9. https://doi.org/10.1016/j.joms.2023.03.007.

[11] Saccomanno S, Deli R, Di Cintio G, De Corso E, Paludetti G, Grippaudo C. Retrospective epidemiological study of mandibular rotational types in patients with orthodontical malocclusion. 2018. https://doi.org/10.14639/0392-100X-1682.

[12] Saccomanno S, Greco F, De Corso E, Lucidi D, Deli R, D'Addona A, Paludetti G. Eagle's syndrome, from clinical presentation to diagnosis and surgical treatment:

a case report. Acta Otorhinolaryngol Ital Organo Uff Della Soc Ital Otorinolaringol E Chir Cerv-facc 2018;38:166–9. https://doi.org/10.14639/0392-100X-1479.
[13] Paolantonio E, Ludovici N, Saccomanno S, La Torre G, Grippaudo C. Association between oral habits, mouth breathing and malocclusion in Italian preschoolers. Eur J Paediatr Dent 2019;20:204–8. https://doi.org/10.23804/ejpd.2019.20.03.07.
[14] Inchingolo AD. Correlation between occlusal trauma and oral microbiota: a microbiological investigation. J Biol Regul Homeost Agents 2021;35. https://doi.org/10.23812/21-2supp1-29.
[15] Inchingolo AD, Malcangi G, Inchingolo AM, Piras F, Settanni V, Garofoli G, Palmieri G, Ceci S, Patano A, De Leonardis N, et al. Benefits and implications of resveratrol supplementation on microbiota modulations: a systematic review of the literature. Int J Mol Sci 2022;23:4027. https://doi.org/10.3390/ijms23074027.
[16] Grippaudo C, Paolantonio EG, Antonini G, Saulle R, La Torre G, Deli R. Association between oral habits, mouth breathing and malocclusion. Acta Otorhinolaryngol Ital Organo Uff Della Soc Ital Otorinolaringol E Chir Cerv-facc 2016;36:386–94. https://doi.org/10.14639/0392-100X-770.
[17] Calixtre LB, Oliveira AB, de Sena Rosa LR, Armijo-Olivo S, Visscher CM, Alburquerque-Sendín F. Effectiveness of mobilisation of the upper cervical region and craniocervical flexor training on orofacial pain, mandibular function and headache in women with TMD. A randomised, controlled trial. J Oral Rehabil 2019;46:109–19. https://doi.org/10.1111/joor.12733.
[18] von Piekartz H, Hall T. Orofacial manual therapy improves cervical movement impairment associated with headache and features of temporomandibular dysfunction: a randomized controlled trial. Man Ther 2013;18:345–50. https://doi.org/10.1016/j.math.2012.12.005.
[19] Grondin F, Hall T, Laurentjoye M, Ella B. Upper cervical range of motion is impaired in patients with temporomandibular disorders. Cranio J Craniomandib Pract 2015;33:91–9. https://doi.org/10.1179/0886963414Z.00000000053.
[20] Grondin F, Hall T. Changes in cervical movement impairment and pain following orofacial treatment in patients with chronic arthralgic temporomandibular disorder with pain: a prospective case series. Physiother Theory Pract 2017;33:52–61. https://doi.org/10.1080/09593985.2016.1247934.
[21] Inchingolo AD, Malcangi G, Semjonova A, Inchingolo AM, Patano A, Coloccia G, Ceci S, Marinelli G, Di Pede C, Ciocia AM, et al. Oralbiotica/Oralbiotics: the impact of oral microbiota on dental health and demineralization: a systematic review of the literature. Children 2022;9:1014. https://doi.org/10.3390/children9071014.
[22] Messina G. The tongue, mandible, hyoid system. Eur J Transl Myol 2017;27:6363. https://doi.org/10.4081/ejtm.2017.6363.
[23] Kondo E. Features and treatment of skeletal class III malocclusion with severe lateral mandibular shift and asymmetric vertical dimension. World J Orthod 2004;5:9–24.
[24] O'Shaughnessy T. Craniomandibular/temporomandibular/cervical implications of a forced hyper-extension/hyper-flexion episode (i.e., whiplash). Funct Orthod 1994;11:5–10. 12.
[25] Malcangi G, Inchingolo AM, Casamassima L, Trilli I, Ferrante L, Inchingolo F, Palermo A, Inchingolo AD, Dipalma G. Effectiveness of herbal medicines with anti-inflammatory, antimicrobial, and antioxidant properties in improving oral health and treating gingivitis and periodontitis: a systematic review. Nutrients 2025;17:762. https://doi.org/10.3390/nu17050762.
[26] Malcangi G, Marinelli G, Inchingolo AD, Trilli I, Ferrante L, Casamassima L, Nardelli P, Inchingolo F, Palermo A, Inchingolo AM, et al. Salivaomics: new frontiers in studying the relationship between periodontal disease and alzheimer's disease. Metabolites 2025;15:389. https://doi.org/10.3390/metabo15060389.
[27] Saccomanno S, Pirino A, Bianco G, Paskay LC, Mastrapasqua R, Scoppa F. Does a short lingual frenulum affect body posture? Assessment of posture in the sagittal plane before and after laser frenulotomy: a pilot study. J Biol Regul Homeost Agents 2021;35:185–95. https://doi.org/10.23812/21-3supp1-21.
[28] Murias I, Grzech-Leśniak K, Murias A, Walicka-Cupryś K, Dominiak M, Golob Deeb J, Matys J. Efficacy of various laser wavelengths in the surgical treatment of Ankyloglossia: a systematic review. Life 2022;12:558. https://doi.org/10.3390/life12040558.
[29] Aras MH, Göregen M, Güngörmüş M, Akgül HM. Comparison of diode laser and Er:YAG lasers in the treatment of Ankyloglossia. Photomed Laser Surg 2010;28:173–7. https://doi.org/10.1089/pho.2009.2498.
[30] Fioravanti M, Zara F, Vozza I, Polimeni A, Sfasciotti GL. The efficacy of lingual laser frenectomy in pediatric OSAS: a randomized double-blinded and controlled clinical study. Int J Environ Res Publ Health 2021;18:6112. https://doi.org/10.3390/ijerph18116112.
[31] Gelb M, Montrose J, Paglia L, Saccomanno S, Quinzi V, Marzo G. Myofunctional therapy part 2: prevention of dentofacial disorders. Eur J Paediatr Dent 2021;22:163–7. https://doi.org/10.23804/ejpd.2021.22.02.15.
[32] Frey L, Green S, Fabbie P, Hockenbury D, Foran M, Elder K. The essential role of the com in the management of sleep-disordered breathing: a literature review and discussion. Int J Orofac Myol Off Publ Int Assoc Orofac Myol 2014;40:42–55.
[33] Inchingolo AD, Marinelli G, Bassi P, Lagioia R, Inchingolo F, Vinjolli F, Palermo A, Celli D, Inchingolo AM, Dipalma G. Comparison of skeletal and airway changes between subjects with class II malocclusion treated with functional therapy in the pre-pubertal and pubertal phases. Eur J Paediatr Dent 2025;26:255–67. https://doi.org/10.23804/ejpd.2025.2544.
[34] Saccomanno S, Saran S, Messore A, Pirino A, Fontanella R, Bruno G, Scoppa F. A new approach for pain in temporomandibular disorders addressing the interaction of diet, eating habits and medications. 2025. https://doi.org/10.58240/1829006X-2025.3-165.
[35] Saccomanno S, Saran S, Vanella V, Mastrapasqua RF, Capogreco M, Carretta G, Pirino A, Scoppa F. Is there any correlation between malocclusion, temporomandibular disorders, and systemic disease? The Importance of Differential Diagnosis 2022.
[36] Inchingolo AM, Inchingolo AD, Fatone MC, Ferrante L, Casamassima L, Trilli I, Inchingolo F, Palermo A, Dipalma G. The effect of periodontal treatment on helicobacter pylori-infection: a systematic review. Periodontal Implant Res 2025;9:3. https://doi.org/10.1007/s41894-025-00146-x.
[37] Patwardhan V, Gil GF, Arrieta A, Cagney J, DeGraw E, Herbert ME, Khalil M, Mullany EC, O'Connell EM, Spencer CN, et al. Differences across the lifespan between females and males in the top 20 causes of disease burden globally: a systematic analysis of the global burden of disease study 2021. Lancet Public Health 2024;9:e282–94. https://doi.org/10.1016/S2468-2667(24)00053-7.
[38] Laverty AA, Been JV. Two simple ways for governments to clear the air for children. Lancet Public Health 2020;5:e465–6. https://doi.org/10.1016/S2468-2667(20)30184-5.
[39] Tran C, Ghahreman K, Huppa C, Gallagher JE. Management of temporomandibular disorders: a rapid review of systematic reviews and guidelines. Int J Oral Maxillofac Surg 2022;51:1211–25. https://doi.org/10.1016/j.ijom.2021.11.009.
[40] Al-Moraissi EA, Wolford LM, Ellis E, Neff A. The hierarchy of different treatments for arthrogenous temporomandibular disorders: a network meta-analysis of randomized clinical trials. J Cranio-Maxillo-fac Surg Off Publ Eur Assoc Cranio-Maxillo-fac Surg 2020;48:9–23. https://doi.org/10.1016/j.jcms.2019.10.004.
[41] Singh BP, Singh N, Jayaraman S, Kirubakaran R, Joseph S, Muthu MS, Jivnani H, Hua F. Occlusal interventions for managing temporomandibular disorders. Cochrane Database Syst Rev 2024;9:CD012850. https://doi.org/10.1002/14651858.CD012850.pub2.
[42] Liu F, Steinkeler A. Epidemiology, diagnosis, and treatment of temporomandibular disorders. Dent Clin 2013;57:465–79. https://doi.org/10.1016/j.cden.2013.04.006.
[43] Guarda-Nardini L, Stifano M, Brombin C, Salmaso L, Manfredini D. A one-year case series of arthrocentesis with hyaluronic acid injections for temporomandibular joint osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:e14–22. https://doi.org/10.1016/j.tripleo.2006.12.021.
[44] Manfredini D, Bonnini S, Arboretti R, Guarda-Nardini L. Temporomandibular joint osteoarthritis: an open label trial of 76 patients treated with arthrocentesis plus hyaluronic acid injections. Int J Oral Maxillofac Surg 2009;38:827–34. https://doi.org/10.1016/j.ijom.2009.03.715.
[45] Inchingolo AD, Laforgia A, Inchingolo AM, Latini G, Pezzolla C, Nardelli P, Palermo A, Inchingolo F, Malcangi G, Dipalma G. Rapid palate expansion's impact on nasal breathing: a systematic review. Int J Pediatr Otorhinolaryngol 2025;190:112248. https://doi.org/10.1016/j.ijporl.2025.112248.
[46] Inchingolo F, Inchingolo AD, Latini G, Trilli I, Ferrante L, Nardelli P, Malcangi G, Inchingolo AM, Mancini A, Palermo A, et al. The role of curcumin in oral health and diseases: a systematic review. Antioxid Basel Switz 2024;13:660. https://doi.org/10.3390/antiox13060660.
[47] Minervini G, Nucci L, Barillari MR, Rotolo RP, Grassia V, d'Apuzzo F. Evaluation of tinnitus in patients with temporomandibular disorders through axis II of the diagnostic criteria for temporomandibular disorders (DC/TMD) and the Tinnitus Handicap Inventory (THI). J Oral Rehabil 2024;51:1158–65. https://doi.org/10.1111/joor.13687.
[48] Warzocha J, Gadomska-Krasny J, Mrowiec J. Etiologic factors of temporomandibular disorders: a systematic review of literature containing diagnostic criteria for temporomandibular disorders (DC/TMD) and research diagnostic criteria for temporomandibular disorders (RDC/TMD) from 2018 to 2022. Healthcare 2024;12:575. https://doi.org/10.3390/healthcare12050575.
[49] Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet J-P, List T, Svensson P, Gonzalez Y, Lobbezoo F, et al. Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: recommendations of the international RDC/TMD consortium network* and orofacial pain special interest group. J Oral Facial Pain Headache 2014;28:6–27. https://doi.org/10.11607/jop.1151.
[50] Dworkin SF, LeResche L, Dworkin SF, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–55.
[51] Minervini G, Franco R, Marrapodi MM, Crimi S, Badnjević A, Cervino G, Bianchi A, Cicciù M, Minervini G, Franco R, et al. Correlation between temporomandibular disorders (TMD) and posture evaluated trough the diagnostic criteria for temporomandibular disorders (DC/TMD): a systematic review with meta-analysis. J Clin Med 2023;12:6991.
[52] Minervini G, Franco R, Marrapodi MM, Fiorillo L, Cervino G, Cicciù M, Minervini G, Franco R, Marrapodi MM, Fiorillo L, et al. Prevalence of temporomandibular disorders in children and adolescents evaluated with diagnostic criteria for temporomandibular disorders: a systematic review with meta-analysis. J Oral Rehabil 2023;50:522–30.
[53] Rammelsberg P, LeResche L, Dworkin S, Mancl L, Rammelsberg P, LeResche L, Dworkin S, Mancl L. Longitudinal outcome of temporomandibular disorders: a 5-Year epidemiologic study of muscle disorders defined by research diagnostic criteria for temporomandibular disorders. J Orofac Pain 2003;17:9–20.
[54] Inchingolo AM, Inchingolo AD, Nardelli P, Latini G, Trilli I, Ferrante L, Malcangi G, Palermo A, Inchingolo F, Dipalma G. Stem cells: present understanding and prospects for regenerative dentistry. J Funct Biomater 2024;15:308. https://doi.org/10.3390/jfb15100308.
[55] Zafar A, Khatoon S, Khan MJ, Abu J, Naeem A. Advancements and limitations in traditional anti-cancer therapies: a comprehensive review of surgery,

chemotherapy, radiation therapy, and hormonal therapy. Discov Oncol 2025;16: 607. https://doi.org/10.1007/s12672-025-02198-8.
[56] Messina G, Amato A, Alioto A, Stallone R, Rizzo F, Ragonese P, Fischetti F, Genua D, Francavilla V, Iovane A, et al. A new road to improve vitamin D and balance through taopatch® and proprioceptive protocol in multiple sclerosis patients. Eur J Transl Myol 2022;32:10774. https://doi.org/10.4081/ejtm.2022.10774.
[57] Carbonari B, Balducci F, Cesaretti G, Cesanelli L, Botticelli D, Messina G. Performance, balance and posture variations with occlusal splint and taopatch® devices: a retrospettive cross-over study. J Sports Med Phys Fitness 2021;61: 317–23. https://doi.org/10.23736/S0022-4707.20.11053-3.
[58] Faizullin I, Faizullina E. Effects of balance training on post-sprained ankle joint instability. Int J Risk Saf Med 2015;27(Suppl 1):S99–101. https://doi.org/10.3233/JRS-150707.
[59] Ben Moussa Zouita A, Majdoub O, Ferchichi H, Grandy K, Dziri C, Ben Salah FZ. The effect of 8-Weeks proprioceptive exercise program in postural sway and isokinetic strength of ankle sprains of Tunisian athletes. Ann Phys Rehabil Med 2013;56:634–43. https://doi.org/10.1016/j.rehab.2013.08.003.
[60] Fu ASN, Hui-Chan CWY. Ankle joint proprioception and postural control in basketball players with bilateral ankle sprains. Am J Sports Med 2005;33: 1174–82. https://doi.org/10.1177/0363546504271976.
[61] de Vasconcelos GS, Cini A, Sbruzzi G, Lima CS. Effects of proprioceptive training on the incidence of ankle sprain in athletes: systematic review and meta-analysis. Clin Rehabil 2018;32:1581–90. https://doi.org/10.1177/0269215518788683.
[62] Burger M, Dreyer D, Fisher RL, Foot D, O'Connor DH, Galante M, Zalgaonkir S. The effectiveness of proprioceptive and neuromuscular training compared to bracing in reducing the recurrence rate of ankle sprains in athletes: a systematic review and meta-analysis. J Back Musculoskelet Rehabil 2018;31:221–9. https://doi.org/10.3233/BMR-170804.
[63] Inchingolo F, Inchingolo AM, Avantario P, Settanni V, Fatone MC, Piras F, Di Venere D, Inchingolo AD, Palermo A, Dipalma G. The effects of periodontal treatment on rheumatoid arthritis and of anti-rheumatic drugs on periodontitis: a systematic review. Int J Mol Sci 2023;24:17228. https://doi.org/10.3390/ijms242417228.
[64] Inchingolo AD, Pezzolla C, Patano A, Ceci S, Ciocia AM, Marinelli G, Malcangi G, Montenegro V, Cardarelli F, Piras F, et al. Experimental analysis of the use of cranial electromyography in athletes and clinical implications. Int J Environ Res Publ Health 2022;19:7975. https://doi.org/10.3390/ijerph19137975.
[65] Inchingolo F, Cantore S, Dipalma G, Georgakopoulos I, Almasri M, Gheno E, Motta A, Marrelli M, Farronato D, Ballini A, et al. Platelet rich fibrin in the management of medication-related osteonecrosis of the jaw: a clinical and histopathological evaluation. J Biol Regul Homeost Agents 2017;31:811–6.
[66] Morris CJ, Aeschbach D, Scheer FAJL. Circadian system, sleep and endocrinology. Mol Cell Endocrinol 2012;349:91–104. https://doi.org/10.1016/j.mce.2011.09.003.
[67] Tonsfeldt KJ, Chappell PE. Clocks on top: the role of the circadian clock in the hypothalamic and pituitary regulation of endocrine physiology. Mol Cell Endocrinol 2012;349:3–12. https://doi.org/10.1016/j.mce.2011.07.003.
[68] Reddy AB, O'Neill JS. Healthy clocks, healthy body, healthy mind. Trends Cell Biol 2010;20:36–44. https://doi.org/10.1016/j.tcb.2009.10.005.
[69] Hanci D, Onaran Öİ. Trismus: definition, causes, and treatment. In: Physical therapy and rehabilitation in otorhinolaryngology. Cham: Springer; 2025. p. 1–6. ISBN 978-3-031-90347-2.
[70] Santiago-Rosado LM, Lewison CS. Trismus. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
[71] Santiago-Rosado LM, Lewison CS, Trismus. In StatPearls; StatPearls Publishing: Treasure Island (FL). In: ; 2025.
[72] Liu B, Zhou H, Tan L, Siu KTH, Guan X-Y. Exploring treatment options in cancer: tumor treatment strategies. Signal Transduct Targeted Ther 2024;9:175. https://doi.org/10.1038/s41392-024-01856-7.
[73] Fares J, Ahmed AU, Ulasov IV, Sonabend AM, Miska J, Lee-Chang C, Balyasnikova IV, Chandler JP, Portnow J, Tate MC, et al. Neural stem cell delivery of an oncolytic adenovirus in newly diagnosed malignant glioma: a First-in-Human, phase 1, dose-escalation trial. Lancet Oncol 2021;22:1103–14. https://doi.org/10.1016/S1470-2045(21)00245-X.
[74] Dipalma G, Inchingolo AM, Lauria P, Marotti P, Chieppa S, Di Venere D, Palermo A, Corsalini M, Inchingolo F, Inchingolo AD. Laser therapy versus conventional treatments in oral leukoplakia: a systematic review of efficacy, recurrence, and postoperative outcomes. Int J Dent 2026;2026:2130179. https://doi.org/10.1155/ijod/2130179.
[75] Inchingolo AD, Marinelli G, Zaminga LP, Savino A, Dell'Anna FE, Inchingolo F, Tartaglia GM, Fabbro MD, Palermo A, Venere DD, et al. Effectiveness of anti-inflammatory premedication on inferior alveolar nerve block success in acute irreversible pulpitis: a systematic review. Explor Med 2026;7:1001381. https://doi.org/10.37349/emed.2026.1001381.
[76] Giannini L, Macrì F, Cattaneo G, Dipalma G, Inchingolo F, Maspero C. Self-perceived vs. clinically assessed malocclusion in adolescents: a cross-sectional study. Appl Sci 2026;16:3822. https://doi.org/10.3390/app16083822.
[77] Malik S, Muhammad K, Waheed Y. Nanotechnology: a revolution in modern industry. Molecules 2023;28:661. https://doi.org/10.3390/molecules28020661.
[78] Zelzer M, Ulijn RV. Next-generation peptide nanomaterials: molecular networks, interfaces and supramolecular functionality. Chem Soc Rev 2010;39:3351–7. https://doi.org/10.1039/c0cs00035c.
[79] McNeil SE. Nanotechnology for the biologist. J Leukoc Biol 2005;78:585–94. https://doi.org/10.1189/jlb.0205074.
[80] Arora S, Rajwade JM, Paknikar KM. Nanotoxicology and in vitro studies: the need of the hour. Toxicol Appl Pharmacol 2012;258:151–65. https://doi.org/10.1016/j.taap.2011.11.010.
[81] Taillard J, Gronfier C, Bioulac S, Philip P, Sagaspe P. Sleep in normal aging, homeostatic and circadian regulation and vulnerability to sleep deprivation. Brain Sci 2021;11:1003. https://doi.org/10.3390/brainsci11081003.
[82] Cajochen C, Münch M, Knoblauch V, Blatter K, Wirz-Justice A. Age-related changes in the circadian and homeostatic regulation of human sleep. Chronobiol Int 2006;23:461–74. https://doi.org/10.1080/07420520500545813.
[83] Inchingolo F, Martelli FS, Gargiulo Isacco C, Borsani E, Cantore S, Corcioli F, Boddi A, Nguyễn KCD, De Vito D, Aityan SK, et al. Chronic periodontitis and immunity, towards the implementation of a personalized medicine: a translational research on gene single nucleotide polymorphisms (SNPs) linked to chronic oral dysbiosis in 96 caucasian patients. Biomedicines 2020;8:115. https://doi.org/10.3390/biomedicines8050115.
[84] Inchingolo AD, Inchingolo AM, Bordea IR, Xhajanka E, Romeo DM, Romeo M, Zappone CMF, Malcangi G, Scarano A, Lorusso F, et al. The effectiveness of osseodensification drilling protocol for implant site osteotomy: a systematic review of the literature and meta-analysis. Materials 2021;14:1147. https://doi.org/10.3390/ma14051147.
[85] Lanzafame RJ. Editorial: good vibrations: more evidence of reciprocity? Photomed Laser Surg 2007;25:465–6. https://doi.org/10.1089/pho.2007.9981.
[86] Bagnato VS, Rodrigues TZ, Garcia V, Vidotti HGM, Aquino Junior AE. de Systemic effects of photobiomodulation and ultrasound as a potentiating tool in the treatment of sleep disorders: pilot study. J Nov Physiother 2024;14:1000703. 1.
[87] Bagnato VS, Rodrigues VP. Mechanical model for the electro-conductivity in metals: temperature effects. Rev Bras Ensino Física 2006;28:35–9.
[88] Weichenthal M, Schwarz T. Phototherapy: how does UV work? Photodermatol Photoimmunol Photomed 2005;21:260–6. https://doi.org/10.1111/j.1600-0781.2005.00173.x.
[89] Weichenthal M, Schwarz T. Phototherapy: How Does UV Work? Life Fast Lane • LITFL 2005;21:260–6.
[90] Beissert S, Schwarz T. Role of immunomodulation in diseases responsive to phototherapy. Methods 2002;28:138–44. https://doi.org/10.1016/s1046-2023(02)00217-7.
[91] Dipalma G, Inchingolo AM, Palumbo I, Guglielmo M, Riccaldo L, Morolla R, Inchingolo F, Palermo A, Charitos IA, Inchingolo AD. Surgical management of pediatric obstructive sleep apnea: efficacy, outcomes, and Alternatives-A systematic review. Life Basel Switz 2024;14:1652. https://doi.org/10.3390/life14121652.
[92] Charitos IA, Marinelli G, Inchingolo AD, Scacco A, Calò F, Ciocia C, Inchingolo F, Scacco S, Palermo A, Severino M, et al. Probiotic modulation of the athletic gut: implications for intestinal barrier function, immunity and exercise-related stress. Ann Oral Maxillofac Surg 2026;22:100670. https://doi.org/10.1016/j.adoms.2026.100670.
[93] Dipalma G, Marinelli G, Ferrante L, Trilli I, Di Serio S, Bassi P, Inchingolo F, Palermo A, Inchingolo AM, Inchingolo AD. The tooth transformer® revolution: autologous dentin biomaterials and platelet concentrates in oral regeneration. A parallel narrative systematic review. Front Dent Med 2026;6. https://doi.org/10.3389/fdmed.2025.1750541.
[94] Association between bone density and maxillary canine impaction: a CBCT-based study. Available online: https://www.mdpi.com/2077-0383/15/2/776. [Accessed 12 May 2026].
[95] Saccomanno S, Stoichkova V, Ederli LS, Guercio-Monaco E, Messina G. Evaluation of the effectiveness of a new nanotechnological device as a support in the management of TMD in young and adult patient. 2025.
[96] Alghamdi MA, Fallica AN, Virzì N, Kesharwani P, Pittalà V, Greish K. The promise of nanotechnology in personalized medicine. J Pers Med 2022;12:673. https://doi.org/10.3390/jpm12050673.
[97] Campoli F, Orofino F, Messina G, Corrado DD, Francavilla VC. Enhancing sleep quality: the impact of the "Repose Tao" pillow with taopatch® nanotechnology—A pilot study. Clocks Sleep 2025;7:32. https://doi.org/10.3390/clockssleep7030032.
[98] Helvig A, Wade S, Hunter-Eades L. Rest and the associated benefits in restorative sleep: a concept analysis. J Adv Nurs 2016;72:62–72. https://doi.org/10.1111/jan.12807.
[99] Messina G, Amato A, Alioto A, Stallone R, Rizzo F, Ragonese P, Fischetti F, Genua D, Francavilla V, Iovane A, et al. A new road to improve vitamin D and balance through taopatch® and proprioceptive protocol in multiple sclerosis patients. Eur J Transl Myol 2022;32:10774. https://doi.org/10.4081/ejtm.2022.10774.
[100] Bose P, Hou J, Thompson FJ. Traumatic brain injury (TBI)-induced spasticity: neurobiology, treatment, and rehabilitation. In: Kobeissy FH, editor. Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects. Boca Raton (FL): Frontiers in Neuroengineering; CRC Press/Taylor & Francis; 2015. ISBN 978-1-4665-6598-2.
[101] Laskowski RA, Creed JA, Raghupathi R. Pathophysiology of mild TBI: implications for altered signaling pathways. In: Kobeissy FH, editor. Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects. Boca Raton (FL): Frontiers in Neuroengineering; CRC Press/Taylor & Francis; 2015. ISBN 978-1-4665-6598-2.
[102] Chandra N, Sundaramurthy A. Acute pathophysiology of blast injury—from biomechanics to experiments and computations: implications on head and polytrauma. In: Kobeissy FH, editor. Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects. Boca Raton (FL): Frontiers in Neuroengineering; CRC Press/Taylor & Francis; 2015. ISBN 978-1-4665-6598-2.

[103] Inchingolo AD, Cazzolla AP, Di Cosola M, Greco Lucchina A, Santacroce L, Charitos IA, Topi S, Malcangi G, Hazballa D, Scarano A, et al. The integumentary system and its microbiota between health and disease. J Biol Regul Homeost Agents 2021;35:303–21. https://doi.org/10.23812/21-2supp1-30.
[104] Crincoli V, Piancino MG, Iannone F, Errede M, Di Comite M. Temporomandibular disorders and oral features in systemic lupus erythematosus patients: an observational study of symptoms and signs. Int J Med Sci 2020;17:153–60. https://doi.org/10.7150/ijms.38914.
[105] Li Y, Zhan Q, Bao M, Yi J, Li Y. Biomechanical and biological responses of periodontium in orthodontic tooth movement: Up-date in a new decade. Int J Oral Sci 2021;13:20. https://doi.org/10.1038/s41368-021-00125-5.
[106] Habib S. Assessment of the therapeutic potential of a dental probiotic in orthodontic patients affected by gingivitis: a randomized control trial. 2016.
[107] Hoffstedt T, Skov Hansen LB, Twetman S, Sonesson M. Effect of an enzyme-containing mouthwash on the dental biofilm and salivary microbiome in patients with fixed orthodontic appliances: a randomized placebo-controlled pilot trial. Eur J Orthod 2023;45:96–102. https://doi.org/10.1093/ejo/cjac062.
[108] Adamo D, Canfora F, Calabria E, Coppola N, Leuci S, Pecoraro G, Cuocolo R, Ugga L, D'Aniello L, Aria M, et al. White matter hyperintensities in burning mouth syndrome assessed according to the age-related white matter changes scale. Front Aging Neurosci 2022;14:923720. https://doi.org/10.3389/fnagi.2022.923720.
[109] Tsai S-R, Hamblin MR. Biological effects and medical applications of infrared radiation. J Photochem Photobiol B 2017;170:197–207. https://doi.org/10.1016/j.jphotobiol.2017.04.014.
[110] Hamblin MR. Photobiomodulation or low-level laser therapy. J Biophotonics 2016;9:1122–4. https://doi.org/10.1002/jbio.201670113.
[111] Chung H, Dai T, Sharma SK, Huang Y-Y, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (Light) therapy. Ann Biomed Eng 2012;40:516–33. https://doi.org/10.1007/s10439-011-0454-7.
[112] Limongelli L, Dipalma G, Favia G, Di Giulio Cesare M, Longo M, Di Serio S, Trilli I, Ferrante L, Inchingolo F, Di Venere D, et al. Temporary Anchorage devices in the infrazygomatic crest: Systematic review of placement guidelines and clinical case series. Ann Oral Maxillofac Surg 2026;22:100660. https://doi.org/10.1016/j.adoms.2026.100660.
[113] The role of astaxanthin as an antioxidant and anti-inflammatory agent in human health: a systematic review - PMC. Available online: https://pmc.ncbi.nlm.nih.gov/articles/PMC12840775/. [Accessed 12 May 2026].
[114] Inchingolo AD, Marinelli G, Limongelli L, Inchingolo F, Favia G, Ferrante L, Di Noia A, Maspero C, Palermo A, Inchingolo AM, et al. Dietary and complementary oral supplements for the management of chronic diseases in children: a systematic review. Front Pediatr 2026;13. https://doi.org/10.3389/fped.2025.1710200.
[115] Karu T. Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP. Photomed Laser Surg 2010;28:159–60. https://doi.org/10.1089/pho.2010.2789.
[116] (PDF) nanomaterials: a review of synthesis, properties, recent progress, and challenges. ResearchGate, doi:10.1039/D0MA00807A.
[117] Ohrbach R, Dworkin SF. The evolution of TMD diagnosis: past, present, future. J Dent Res 2016;95:1093–101. https://doi.org/10.1177/0022034516653922.
[118] Truelove E, Pan W, Look JO, Mancl LA, Ohrbach RK, Velly AM, Huggins KH, Lenton P, Shiffman EL. The research diagnostic criteria for temporomandibular disorders. III: validity of axis I diagnoses. J Orofac Pain 2010;24:35–47.
[119] Çetiner RB, Ergün-Kunt G, Yüceer-Çetiner E, Schimmel M. Masticatory function before and after masticatory muscle-related temporomandibular disorder treatment: an observational study. J Oral Rehabil 2022;49:295–300. https://doi.org/10.1111/joor.13286.
[120] Dworkin SF, Huggins KH, LeResche L, Von Korff M, Howard J, Truelove E, Sommers E. Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. J Am Dent Assoc 1990;120:273–81. https://doi.org/10.14219/jada.archive.1990.0043.
[121] Gesch D, Bernhardt O, Alte D, Schwahn C, Kocher T, John U, Hensel E. Prevalence of signs and symptoms of temporomandibular disorders in an urban and rural German population: results of a population-based study of health in Pomerania. Quintessence Int 2004;35:143–50.
[122] Costa YM, Ariji Y, Ferreira DMaO, Bonjardim LR, Conti PCR, Ariji E, Svensson P. Muscle hardness and masticatory myofascial pain: assessment and clinical relevance. J Oral Rehabil 2018;45:640–6. https://doi.org/10.1111/joor.12644.
[123] Inchingolo F, Tatullo M, Abenavoli FM, Marrelli M, Inchingolo AD, Corelli R, Inchingolo AM, Dipalma G. Surgical treatment of depressed scar: a simple technique. Int J Med Sci 2011;8:377–9. https://doi.org/10.7150/ijms.8.377.
[124] (PDF) using nanotechnology to improve pain and function with a novel, drug-free, topical pain-relief patch: an interim analysis. ResearchGate.
[125] Gudin JA, Dietze DT, Hurwitz PL. Improvement of pain and function after use of a topical pain relieving patch: results of the RELIEF study. J Pain Res 2020;13:1557–68. https://doi.org/10.2147/JPR.S258883.
[126] Gudin J, Dietze D, Hurwitz P. Using A novel, non-drug, topical pain-relief patch to improve pain and function: final analysis of the PREVENT study. Anesth Pain Res 2022;6. https://doi.org/10.33425/2639-846X.1059.
[127] Kongsgaard U, Kaasa S, Dale O, Ottesen S, Nordøy T, Hessling SE, von Hofacker S, Bruland ØS, Lyngstadaas A. *Palliative treatment of cancer-related pain*; NIPH systematic reviews: executive summaries; knowledge centre for the health services at the Norwegian Institute of Public Health (NIPH): oslo, Norway. 2005. ISBN 978-82-8121-074-5.
[128] Gudin JA, Brennan MJ, Harris ED, Hurwitz PL, Dietze DT, Strader JD. Changes in pain and concurrent pain medication use following compounded topical analgesic treatment for chronic pain: 3- and 6-Month Follow-up results from the prospective, observational optimizing patient experience and response to topical analgesics study. J Pain Res 2017;10:2341–54. https://doi.org/10.2147/JPR.S143513.
[129] Mohammadi I, Adibparsa M, Yashooa RKh, Sehat MS, Sadeghi M. Effect of continuous positive airway pressure therapy on blood levels of IL-6, IL-10, IL-18, IL-1β, IL-4, and IL-17 in obstructive sleep apnoea adults: a systematic review, meta-analysis and trial sequential analysis. Int Orthod 2024;22:100917. https://doi.org/10.1016/j.ortho.2024.100917.
[130] Gupta R, Pandi-Perumal SR, Almeneessier AS, BaHammam AS. Hypersomnolence and traffic safety. Sleep Med Clin 2017;12:489–99. https://doi.org/10.1016/j.jsmc.2017.03.018.
[131] Demirdöğen Çetinoğlu E, Görek Dilektaşlı A, Demir NA, Özkaya G, Acet NA, Durmuş E, Ursavaş A, Karadağ M, Ege E. The relationship between driving simulation performance and obstructive sleep apnoea risk, daytime sleepiness, obesity and road traffic accident history of commercial drivers in Turkey. Sleep Breath Schlaf Atm 2015;19:865–72. https://doi.org/10.1007/s11325-014-1114-6.
[132] Ebrahimi MH, Sadeghi M, Dehghani M, Niiat KS. Sleep habits and road traffic accident risk for Iranian occupational drivers. Int J Occup Med Environ Health 2015;28:305–12. https://doi.org/10.13075/ijomeh.1896.00360.
[133] Garbarino S, Durando P, Guglielmi O, Dini G, Bersi F, Fornarino S, Toletone A, Chiorri C, Magnavita N. Sleep apnea, sleep debt and daytime sleepiness are independently associated with road accidents. A cross-sectional study on truck drivers. PLoS One 2016;11:e0166262. https://doi.org/10.1371/journal.pone.0166262.
[134] (PDF) overview of sleep disorders. In ResearchGate.
[135] Overview of sleep disorders. In: The behavioral, molecular, pharmacological, and clinical basis of the sleep-wake cycle. Academic Press; 2019. p. 103–22.
[136] Saccomanno S, Stoichkova V, Silenzi Ederli L, Guercio-Monaco E, Messina G. Evaluation of the effectiveness of a new nanotechnological device as a support in the management of TMD in young and adult patient. 2025.
[137] Delcanho, R.; Val, M.; Nardini, L.G.; Manfredini, D. Botulinum toxin for treating temporomandibular disorders: what is the evidence? J Oral Facial Pain Headache 36, 3023, doi:10.11607/ofph.3023.
[138] Ohrbach R, Bair E, Fillingim RB, Gonzalez Y, Gordon SM, Lim P-F, Ribeiro-Dasilva M, Diatchenko L, Dubner R, Greenspan JD, et al. Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. J Pain 2013;14:T33–50. https://doi.org/10.1016/j.jpain.2013.07.018.
[139] National academies of sciences, engineering, and medicine; health and medicine division; board on health care services; board on health sciences policy; committee on temporomandibular disorders (TMDs): from research discoveries to clinical treatment *temporomandibular disorders: priorities for research and care*. In: Yost O, Liverman CT, English R, Mackey S, Bond EC, editors. The national academies collection: reports funded by national institutes of health. Washington (DC): National Academies Press (US); 2020. ISBN 978-0-309-67048-7.
[140] Safour W, Hovey R. The impact of chronic temporomandibular disorders on fatigue and daily life: a qualitative phenomenological study. JDR Clin Transl Res 2025;10:398–405. https://doi.org/10.1177/23800844241302064.
[141] Leonid K. Exploring the relationship between temporomandibular disorders and sexual function. Sex Med Rev 2025;13:89–93. https://doi.org/10.1093/sxmrev/qeae063.
[142] Simmons HC. A critical review of Dr. Charles S. Greene's article titled "Managing the Care of Patients with Temporomandibular Disorders: a New Guideline for Care" and a revision of the American association for dental research's 1996 policy statement on temporomandibular disorders, approved by the AADR council in march 2010, published in the journal of the American dental association September 2010. Cranio J Craniomandib Pract 2012;30:9–24. https://doi.org/10.1179/crn.2012.003.
[143] Zhang Y, Zhang H, Liu R, Jin S, Huo T, Wei H, Qin L. The efficacy of treatments for temporomandibular disorders with occlusal splints versus other conservative therapies: a meta-analysis of randomized controlled trials. Oral Surg Oral Med Oral Pathol Oral Radiol 2025;139:509–20. https://doi.org/10.1016/j.oooo.2024.11.089.
[144] Ekici Ö, Dündar Ü, Gökay GD, Büyükbosna M. Evaluation of the efficiency of different treatment modalities in individuals with painful temporomandibular joint disc displacement with reduction: a randomised controlled clinical trial. Br J Oral Maxillofac Surg 2022;60:350–6. https://doi.org/10.1016/j.bjoms.2021.08.001.
[145] Gallagher C, Gallagher V, Whelton H, Cronin M. The normal range of mouth opening in an Irish population. J Oral Rehabil 2004;31:110–6. https://doi.org/10.1046/j.0305-182x.2003.01209.x.
[146] López-Gómez L, Uranga JA. Polyphenols in the prevention and treatment of colorectal cancer: a systematic review of clinical evidence. Nutrients 2024;16:2735. https://doi.org/10.3390/nu16162735.
[147] Del Rio D, Rodriguez-Mateos A, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary (Poly)Phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases. Antioxid Redox Signal 2013;18:1818–92. https://doi.org/10.1089/ars.2012.4581.
[148] Moon YJ, Wang X, Morris ME. Dietary flavonoids: effects on xenobiotic and Carcinogen metabolism. Toxicol Vitro Int J Publ Assoc BIBRA 2006;20:187–210. https://doi.org/10.1016/j.tiv.2005.06.048.
[149] Hagan M, Hayee BH, Rodriguez-Mateos A. (Poly)Phenols in inflammatory bowel disease and irritable bowel syndrome: a review. Molecules 2021;26:1843. https://doi.org/10.3390/molecules26071843.
[150] Nimptsch K, Zhang X, Cassidy A, Song M, O'Reilly ÉJ, Lin JH, Pischon T, Rimm EB, Willett WC, Fuchs CS, et al. Habitual intake of flavonoid subclasses and

risk of colorectal cancer in 2 large prospective cohorts. Am J Clin Nutr 2016;103:184–91. https://doi.org/10.3945/ajcn.115.117507.
[151] Nakaji S, Umeda T, Shimoyama T, Sugawara K, Tamura K, Fukuda S, Sakamoto J, Parodi S. Environmental factors affect Colon carcinoma and rectal carcinoma in men and women differently. Int J Colorectal Dis 2003;18:481–6. https://doi.org/10.1007/s00384-003-0485-0.
[152] Tamakoshi K, Wakai K, Kojima M, Watanabe Y, Hayakawa N, Toyoshima H, Yatsuya H, Kondo T, Tokudome S, Hashimoto S, et al. A prospective study of body size and Colon cancer mortality in Japan: the JACC study. Int J Obes Relat Metab Disord J Int Assoc Study Obe 2004;28:551–8. https://doi.org/10.1038/sj.ijo.0802603.
[153] Crincoli V, De Biase C, Cazzolla AP, Campobasso A, Dioguardi M, Piancino MG, Mattia L, Ribatti D, Di Comite M. Effects of contact sports on temporomandibular disorders: an observational study. Dent J 2022;10:180. https://doi.org/10.3390/dj10100180.
[154] Van Spall HGC, Bastien A, Gersh B, Greenberg B, Mohebi R, Min J, Strauss K, Thirstrup S, Zannad F. The role of early-phase trials and real-world evidence in drug development. Nat Cardiovasc Res 2024;3:110–7. https://doi.org/10.1038/s44161-024-00420-4.
[155] Paraskevas KI, de Borst GJ, Veith FJ. Why randomized controlled trials do not always reflect reality. J Vasc Surg 2019;70:607–614.e3. https://doi.org/10.1016/j.jvs.2019.01.052.
[156] Nguyen J, Li A, Tam DY, Forbes TL. Analysis of spin in vascular surgery randomized controlled trials with nonsignificant outcomes. J Vasc Surg 2022;75:1074–1080.e17. https://doi.org/10.1016/j.jvs.2021.09.051.
[157] Braga LH, Farrokhyar F, Dönmez Mİ, Nelson CP, Haid B, Herbst K, Garriboli M, Cascio S, Nieuwhof-Leppink A, Kaefer M, et al. Randomized controlled trials – the what, when, how and why. J Pediatr Urol 2025;21:397–404. https://doi.org/10.1016/j.jpurol.2024.11.021.
[158] Levasseur M, Chaintré-Prieur A, Dubois M-F, Maisonneuve C, Filiatrault J, Vassiliadis H-M. Strengths, challenges, and strategies for implementing pragmatic multicenter randomized controlled trials (RCTs): example of the personalized citizen assistance for social participation (APIC) trial. Trials 2024;25:415. https://doi.org/10.1186/s13063-024-08248-w.
[159] Limongelli L, Inchingolo AD, Marinelli G, Inchingolo F, Favia G, Casamassima L, Trilli I, Ferrante L, Forte M, Inchingolo AM, et al. The role of human papillomavirus in oral squamous cell and verrucous carcinomas: a systematic review with case series. Oncol Rev 2026;20. https://doi.org/10.3389/or.2026.1798220.
[160] Fernainy P, Cohen AA, Murray E, Losina E, Lamontagne F, Sourial N. Rethinking the pros and cons of randomized controlled trials and observational studies in the era of big data and advanced methods: a panel discussion. BMC Proc 2024;18:1. https://doi.org/10.1186/s12919-023-00285-8.
[161] Real-world data: bridging the gap between clinical trials and practice - eClinicalMedicine. Available online: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(24)00494-2/fulltext. [Accessed 12 May 2026].
[162] Andrade C. Poorly recognized and uncommonly acknowledged limitations of randomized controlled trials. Indian J Psychol Med 2025;47:83–5. https://doi.org/10.1177/02537176241297953.
[163] Zhaori G. Importance of sample size determination for randomized controlled clinical trials for coronavirus disease 2019 antiviral therapies. Pediatr Investig 2024;8:7–11. https://doi.org/10.1002/ped4.12415.
[164] Zhaori G, Lu L, Liu C, Han S, Guo Y. Better design leads to better results - importance of virological outcome design in clinical trials for antiviral treatment of coronavirus disease 2019. Pediatr Investig 2023;7:1–5. https://doi.org/10.1002/ped4.12363.
[165] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the treatment of Covid-19 - Final report. N Engl J Med 2020;383:1813–26. https://doi.org/10.1056/NEJMoa2007764.
[166] Valverde A, Hamilton C, Moro C, Billeres M, Magistretti P, Mitrofanis J. Lights at night: does photobiomodulation improve sleep? Neural Regen Res 2023;18:474. https://doi.org/10.4103/1673-5374.350191.
[167] Ahn JH, Cho H, Kim J-H, Kim SH, Ham J-S, Park I, Suh SH, Hong SP, Song J-H, Hong Y-K, et al. Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. Nature 2019;572:62–6. https://doi.org/10.1038/s41586-019-1419-5.
[168] Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 2015;212:991–9. https://doi.org/10.1084/jem.20142290.
[169] Moro C, Valverde A, Dole M, Hoh Kam J, Hamilton C, Liebert A, Bicknell B, Benabid A-L, Magistretti P, Mitrofanis J. The effect of photobiomodulation on the brain during wakefulness and sleep. Front Neurosci 2022;16:942536. https://doi.org/10.3389/fnins.2022.942536.
[170] Gvilia I. Underlying brain mechanisms that regulate sleep-wakefulness cycles. Int Rev Neurobiol 2010;93:1–21. https://doi.org/10.1016/S0074-7742(10)93001-8.
[171] [neurochemical mechanisms of sleep regulation]. Glas Srp Akad Nauka Umet Odeljenje Med Nauka 2009:97–109.
[172] Steininger TL, Rye DB, Wainer BH. Afferent projections to the cholinergic Pedunculopontine Tegmental Nucleus and adjacent midbrain extrapyramidal area in the albino rat. I. Retrograde tracing studies. J Comp Neurol 1992;321:515–43. https://doi.org/10.1002/cne.903210403.
[173] Dipalma G, Inchingolo AD, Piras F, Palmieri G, Pede CD, Ciocia AM, Siciliani RA, Olio FD, Inchingolo AM, Palermo A, et al. Efficacy of guided autofluorescence laser therapy in MRONJ: a systematic review. Eur Rev Med Pharmacol Sci 2023;27:11817–31. https://doi.org/10.26355/eurrev_202312_34780.
[174] Malik S, Muhammad K, Waheed Y. Emerging applications of nanotechnology in healthcare and medicine. Molecules 2023;28:6624. https://doi.org/10.3390/molecules28186624.
[175] Soleymani-Goloujeh M, Hosseini S, Baghaban Eslaminejad M. Advanced nanotechnology approaches as emerging tools in cellular-based technologies. Adv Exp Med Biol 2023;1409:127–44. https://doi.org/10.1007/5584_2022_725.
[176] Gupta J. Nanotechnology applications in medicine and dentistry. J Investig Clin Dent 2011;2:81–8. https://doi.org/10.1111/j.2041-1626.2011.00046.x.
[177] Soll RF, Ovelman C, McGuire W. The future of cochrane neonatal. Early Hum Dev 2020;150:105191. https://doi.org/10.1016/j.earlhumdev.2020.105191.
[178] Patil M, Mehta DS, Guvva S. Future impact of nanotechnology on medicine and dentistry. J Indian Soc Periodontol 2008;12:34–40. https://doi.org/10.4103/0972-124X.44088.
[179] Inchingolo F, Inchingolo AM, Latini G, Ferrante L, Trilli I, Del Vecchio G, Palmieri G, Malcangi G, Inchingolo AD, Dipalma G. Oxidative stress and natural products in orthodontic treatment: a systematic review. Nutrients 2023;16:113. https://doi.org/10.3390/nu16010113.
[180] Melis M, Di Giosia M, Zawawi KH. Low level laser therapy for the treatment of temporomandibular disorders: a systematic review of the literature. Cranio J Craniomandib Pract 2012;30:304–12. https://doi.org/10.1179/crn.2012.045.
[181] Hasanoğlu Erbaşar G üz N, Türp JC, Hasanoglu Erbasar G üz N, Türp JC. Low-Level Laser therapy for patients with temporomandibular disorders: a synopsis of systematic reviews and Current RCTs. Quintessence Int 2026.
[182] Khoury J, Doghramji K. Primary sleep disorders. Psychiatr Clin 2015;38:683–704. https://doi.org/10.1016/j.psc.2015.08.002.
[183] Elder GJ, Flo-Groeneboom E. How can light be used to optimize sleep and health in older adults? Prog Brain Res 2022;273:331–55. https://doi.org/10.1016/bs.pbr.2022.04.002.
[184] Klerman EB, Duffy JF, Dijk DJ, Czeisler CA. Circadian phase resetting in older people by ocular bright light exposure. J Investig Med Off Publ Am Fed Clin Res 2001;49:30–40. https://doi.org/10.2310/6650.2001.34088.
[185] Shanahan TL, Kronauer RE, Duffy JF, Williams GH, Czeisler CA. Melatonin rhythm observed throughout a three-cycle bright-light stimulus designed to reset the human circadian pacemaker. J Biol Rhythm 1999;14:237–53. https://doi.org/10.1177/074873099129000560.
[186] Laforgia A, Inchingolo AM, Inchingolo F, Sardano R, Trilli I, Di Noia A, Ferrante L, Palermo A, Inchingolo AD, Dipalma G. Paediatric dental trauma: insights from epidemiological studies and management recommendations. BMC Oral Health 2025;25:6. https://doi.org/10.1186/s12903-024-05222-5.