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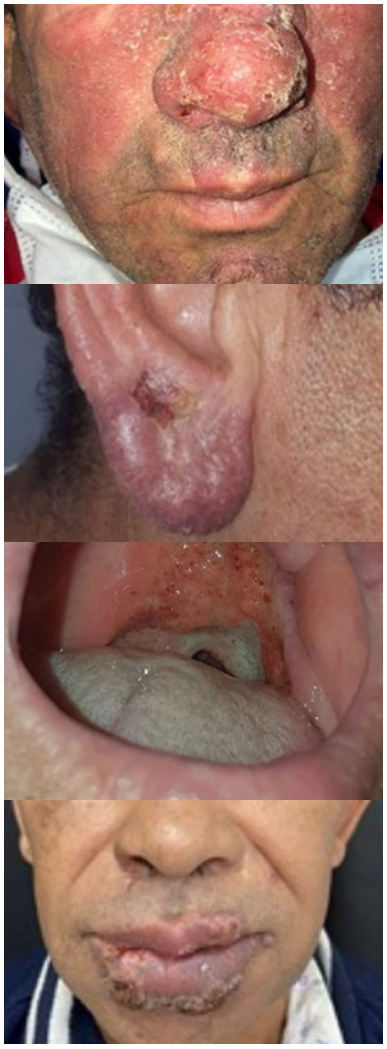

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EDITORIAL

WCD2027: the global dermatology ecosystem gathers in Mexico

WCD2027: el ecosistema dermatológico mundial se reúne en México

Jorge Ocampo-Candiani[1] and Mariel Isa[2]*

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The World Congress of Dermatology (WCD), sponsored by the International League of Dermatological Societies (ILDS), will host its 26th edition in Guadalajara, Mexico, from June 21 to 26, 2027. The venue will be Expo Guadalajara, the largest convention centre in the country and one of the leading venues in Latin America, offering top-quality infrastructure for this global meeting.

The congress will be held under the theme "Discovering the dermatological ecosystem for a diverse and inclusive future". This vision seeks to bring together all stakeholders in the healthcare sector dedicated to scientific collaboration.

Registration is now open, with categories designed to ensure access for the entire sector: from dermatologists and healthcare professionals to residents, students and delegates from low- and middle-income countries, according to the World Bank classification. Until October 31, 2026, interested participants will be able to access early-bird rates. Registration includes full access to the scientific programme, official ceremonies, sponsored symposia and the commercial exhibition area, access to which is reserved exclusively for healthcare professionals.

In addition, ILDS member societies will be able to participate in the Dermathon, an innovative digital initiative for collaborative and competitive participation that strengthens links within the international dermatological network.

The scientific programme will offer an exceptional experience over six days of activity, covering everything from cutting-edge research to daily clinical practice. The academic programme includes five high-level plenary sessions, which will feature keynote lectures and distinguished presentations by the key opinion leaders, as well as 227 symposia and 13 controversy sessions. A total of 19 clinical management workshops have also been added as a new training modality, designed to reinforce the direct application of knowledge in daily dermatological practice.

As part further educational activities, attendees will have access to 24 courses and 4 live course demonstrations. Among these complementary programs, the live course demonstrations are the new feature of this edition.

Professionals may submit their research before September 14, 2026. Selected papers will become part of the scientific programme and may be presented as free communications, resident forums or e-posters, with additional prominent visibility on the event's digital platform.

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Similarly, WCD2027 will award attendance grants to authors attending in person, including residents, fellows, rising stars and specialists from developing countries, as long as they do not receive industry funding, to ensure academic independence.

With the support of more than 20 main sponsors and broad participation from international sponsors and exhibitors, WCD2027 is more than a congress: it is a global meeting point for dermatological science.

We invite you to stay connected through the official event app, available on the App Store and Google Play, and to visit our website to discover all the details.

See you in Guadalajara in 2027!

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ORIGINAL ARTICLE

Clinical profile of patients with cutaneous leishmaniasis treated with pentamidine in Colombia, 2011-2023

Perfil clínico de pacientes con leishmaniasis cutánea tratados con pentamidina en Colombia, 2011-2023

Liliana López-Carvajal[1], Allison T. Montoya-Ordoñez[2], Andrea Morales-Ramírez[2], Jaiberth A. Cardona-Arias[2], and Claudia Cruz[3]*

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Abstract

Background: *Leishmaniasis is classified as one of a group of neglected tropical diseases. These diseases primarily affect low-income populations and present significant gaps in prevention, diagnosis, and treatment. The cutaneous form of the disease is the most common. In addition to the limited options for therapeutic management of the disease, evidence on its clinical profile is very limited.* **Objective:** *The objective of the study is to describe the clinical profile of military patients with cutaneous leishmaniasis treated with pentamidine in Colombia between 2011 and 2023.* **Materials and methods:** *Retrospective cohort study of 91 military personnel treated with intramuscular pentamidine. Administration was carried out under directly observed therapy by medical personnel, who also monitored the evolution of the lesions and the safety profile of the drug for 90 days. Biases were controlled, the analysis was based on frequencies, and the comparison of adverse effects was performed using the McNemar test.* **Results:** *The majority of cases were concentrated in the Amazon and Orinoquia regions, primarily among young people. Ulceration was the predominant lesion (96.7%) and was primarily single (62.6%). The treatment with pentamidine proved to be 100% effective. The local adverse effects were mild, with local infections reported in 9.9% of cases and pain in 7.7%. Systemic adverse effects of treatment were only statistically higher in liver function (increased alanine aminotransferase and aspartate aminotransferase) and kidney function (increased blood urea nitrogen [BUN] and creatinine).* **Conclusions:** *Pentamidine demonstrated high effectiveness with a favorable safety profile. However, alterations in transaminases, BUN, and creatinine were common, suggesting the need to improve medical monitoring to detect complications and improve preventive strategies in disease management.*

Keywords: *Cutaneous leishmaniasis. Pentamidine. Treatment. Safety. Clinical manifestations.*

Resumen

Antecedentes: *La leishmaniasis hace parte del grupo de enfermedades tropicales desatendidas. Estas enfermedades afectan principalmente a poblaciones de bajos ingresos y presentan importantes deficiencias en prevención, diagnóstico y tratamiento. La forma cutánea es la más común. Además de las limitadas opciones para el tratamiento de la enfermedad, los datos sobre su perfil clínico son muy escasos.* **Objetivo:** *Describir el perfil clínico de los pacientes con leishmaniasis cutánea tratados con pentamidina en Colombia entre 2011 y 2023.* **Material y métodos:** *Estudio de cohorte retrospectivo de 91 militares tratados con pentamidina intramuscular. La administración se llevó a cabo bajo terapia directamente*

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observada por personal médico. Seguimiento a evolución de lesiones y perfil de seguridad durante 90 días. Se controlaron los sesgos, el análisis se basó en frecuencias y la comparación de los efectos adversos se realizó mediante la prueba de McNemar. **Resultados:** *La mayoría de los casos se concentraron en las regiones de la Amazonía y la Orinoquia, principalmente en personas jóvenes. Predominaron las lesiones ulceradas (96,7%) y únicas (62,6%). El tratamiento con pentamidina fue 100% efectivo. Efectos adversos locales fueron leves: infecciones locales (9,9%) y dolor (7,7%). Efectos adversos sistémicos fueron estadísticamente superiores función hepática (aumento de ALT y AST) y función renal (aumento de BUN y creatinina).* **Conclusiones:** *La pentamidina demostró una alta eficacia con un perfil de seguridad favorable. Sin embargo, fueron frecuentes las alteraciones en transaminasas, BUN y creatinina, lo que sugiere la necesidad de mejorar la monitorización médica para detectar complicaciones y mejorar las estrategias preventivas en el manejo de la enfermedad.*

Palabras clave: *Leishmanisis cutánea. Pentamidina. Tratamiento. Seguridad. Manifestaciones clínicas.*

Introduction

Leishmaniasis is a disease caused by more than 20 parasitic species of the genus *Leishmania*. At least 90 species of sandflies are known to transmit the parasite through their bite. The disease can present in three clinical forms: visceral, cutaneous, and mucocutaneous.[1]

Cutaneous leishmaniasis (CL) is the most common clinical form of the disease and is widely distributed in regions of East Africa, North Africa, West and Southeast Asia, and the Americas, with a particular concentration in Brazil, Colombia, and Peru.[2] It is present in 100 countries on all continents except Australia and Antarctica, being more common in temperate tropical areas with low economic development.[3] The number of cases per year is estimated to range from 600,000 to 1 million. In some years, approximately 60% of new cases have been concentrated in Afghanistan, Algeria, Brazil, Colombia, Syria, and Iran, with armed conflicts being one of the main factors explaining the increase in cases. Outbreaks have also been the result of human encroachment into forested areas inhabited by sand flies or the exposure of susceptible individuals in endemic areas.[4]

Treatment options include antimonials such as glucantime and second-line drugs such as amphotericin B, miltefosine, and pentamidine, which have demonstrated acceptable efficacy. However, it is essential to carefully consider the safety profiles associated with these medications when selecting a treatment plan. In the case of pentamidine, immediate effects such as hypotension, nausea, vomiting, and syncope have been reported. Systemic effects on glucose metabolism, including hypoglycemia and diabetogenic effects, have also been reported in research conducted on different populations. A study conducted in Colombia examined the efficacy of pentamidine in treating patients with CL and reported an efficacy rate of 96% (23/24) among the patients treated with pentamidine. The most common adverse effects reported were hypotension (8.3%), hypoglycemia (4.2%), headache, and myalgia (4.2%).[5] Meanwhile, a study conducted in Colombia evaluated the tolerance of 63 patients with LC treated with pentamidine isethionate, where 32% (20/63) discontinued treatment and 55.8% (24/43) experienced mild or moderate side effects such as pain at the application site (34.8%), edema at the application site (11.6%), dizziness (11.6%), fever (9.3%), headache (4.6%), adynamia (4.6%), nausea (2.3%), and joint pain (2.3%). In patients who completed treatment, complete cure was observed in 41.9% at 3 weeks and 44.2% at 6 weeks.[6] In a study in Peru of patients with CL caused by *Leishmania braziliensis*, 40 patients received pentamidine (2 mg/kg on alternate days for seven injections) with a cure rate of 35%, 58% failed, and 7% discontinued treatment, with adverse effects mainly of the gastrointestinal and musculoskeletal type.[7]

These findings indicate significant variability in the therapeutic response and safety of pentamidine for the treatment of leishmaniasis. There is also a limited number of studies on this topic, and methodological limitations are evident in these studies. These limitations include a low number of patients included, a registry that is not fully comprehensive in terms of adverse effects, and the absence of additional information on effects on different body systems. These findings demonstrate the need for further studies on patients treated with this therapeutic regimen.

In addition, it is important to highlight that this is a neglected disease and, as such, has been relegated in terms of research and treatment development due to a combination of factors, including a lack of commercial incentive and its low priority on the public health agenda. These diseases tend to affect mainly impoverished and marginalized populations, have a significant impact on the health and well-being of affected communities, but do not receive the attention and

funding they require, resulting in low diagnosis and treatment coverage.[8] Leishmaniasis is among the 20 neglected tropical diseases, according to the World Health Organization.[3]

Accordingly, the objective of this research was to describe the clinical profile of patients treated with pentamidine at military bases in Colombia between 2011 and 2023.

Materials and methods

Type and subjects of study

An observational study was conducted on a retrospective cohort of 91 men with CL treated with intramuscular pentamidine at a dose of 3.3-6.2 mg for 5-10 days, depending on each patient's weight and clinical condition. These patients were adults with previous episodes of leishmaniasis that did not heal with the first cycle of pentavalent antimonials (glucantime) and who voluntarily accepted treatment with pentamidine as a second line of treatment.

Diagnosis

The diagnosis was made by checking for the presence of the parasite using one of the following methods: direct examination (78 patients), biopsy (10 patients), and polymerase chain reaction (PCR) (3 patients).[9,10]

Information collection and bias control

Pentamidine isethionate was administered under directly observed therapy (DOT) by medical personnel, who also monitored the evolution of the lesions and the safety profile of the drug. The information collected included sociodemographic information, disease history, origin data, clinical characterization of lesions, treatment outcomes, side effects with their frequency and severity, and monitoring with paraclinical tests to evaluate hematological (hemoleukogram), renal (creatinine and blood urea nitrogen [BUN]), hepatic (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase), pancreatic (amylase) blood sugar level (glycemia), and cardiac function (electrocardiogram). According to Pan American Health Organization recommendations, the size of the lesions was evaluated up to 90 days to determine the outcomes of cure, reactivation, or therapeutic failure. Cure is defined as complete resolution of the lesions, complete re-epithelialization, flattening of the edges of the lesions, disappearance of induration at the base, disappearance of lymphangitis or adenitis if it had occurred, and absence of new lesions. Relapses were also considered, defined as the reappearance of signs and symptoms of CL at the same site of the treated lesion after it had been cured.[11,12]

To control for selection and information bias, a medical evaluation was performed by physicians with extensive experience in managing the disease, and diagnostic tests were carried out in certified laboratories with internal and external quality control programs. In addition, the database was checked using a random, blind, and independent comparison of 20% of the information on individuals in the population and their physical medical records.

Ethical considerations

The research project was approved by the Research Ethics Committee of the Central Military Hospital (Minutes #3, 2018). The guidelines of the Declaration of Helsinki and Resolution 8430 of the Colombian Ministry of Health, 1993, were followed, according to which this research corresponds to a risk-free study, given that it is based on documentary data. The principles of autonomy, beneficence, non-maleficence, and justice were respected.

Results

Patient characteristics

Most patients were from Guaviare 29.7% (n = 27), Vaupés 15.4% (n = 14), and Meta 11% (n = 10) departments belonging to the Amazon region of Colombia. A high percentage had a history of leishmaniasis (83.5%), of which 85.5% reported having had a single episode. The average age of the participants was 24.1 ± 4.2 years, with an age range between 19 and 41 years (Table 1).

In the characterization of lesions, ulceration was the most prevalent (96.7%, n = 88) and was typically single (62.6%) (Table 2).

Effectiveness

The treatment was found to be 100% effective (Table 2).

Table 1. Description of the study population

Variable	Factors	n	%
Region/ department (province)	Amazonian		
	Guaviare	27	29.7
	Vaupés	14	15.4
	Meta	10	11.0
	Caquetá	8	8.8
	Putumayo	4	4.4
	Guainía	3	3.3
	Caribbean		
	Córdoba	7	7.7
	Pacific		
	Chocó	7	7.7
	Andean		
	Tolima	5	5.5
	Other departments[a]	6	6.6
Ethnicity	Mestizo	80	87.9
	Afro-Colombian	11	12.1
History of leishmaniasis	No	15	16.5
	Yes[b]	76	83.5
	One previous episode	65	85.5
	2-3 previous episodes	11	14.5
Quantitative variable	Mean ± SD[c]	Median (IQR)[d]	Range
Age	24.1 ± 4.2	23 (21-26)	19-41

[a]One case in each of the following departments: Amazonas, Antioquia, Bolívar, Boyacá, Huila, and Nariño.
[b]All previously treated with glucantime.
[c]Standard deviation.
[d]Interquartile range.

Table 2. Characterization of lesions and therapeutic response

Variable	Factors	n	%
Lesions	Ulcer	88	96.7
	Other	3	3.3
	Single	57	62.6
	Two	16	17.6
	Three or four	13	14.3
	Five or seven	5	5.5
Anatomical location	Head and neck	18	14.4
	Thorax	13	10.4
	Upper limbs	69	55.2
	Lower limbs	25	20
Outcome	Cure	91	100
	Reactivation	0	0.0
	Therapeutic failure	0	0.0

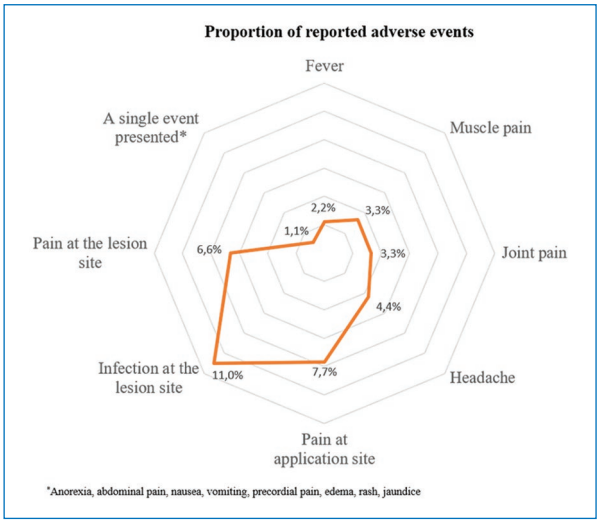

Figure 1. Adverse effects under medical evaluation.

Safety

26.4% (24/91) of patients experienced at least one adverse event. Primary safety concerns identified in the medical evaluation were mild and local, including infection (9.9%), pain at the treatment site (7.7%), and headache (4.4%). The clinical evaluation revealed no indications of pancreatitis, acute renal failure, or liver dysfunction (Fig. 1 and Table 2).

In the analysis of systemic adverse effects, statistically higher proportions were only found at the end of treatment in liver function (increased ALT and AST) and kidney function (increased BUN and creatinine) (Table 3).

Discussion

Most patients were from Guaviare, Vaupés, and Meta departments belonging to the Amazon region of Colombia, where the species *L. braziliensis* predominates.[13,14] This finding coincides with the report by Salgado-Almario et al., who documented the highest incidence in Guaviare. The study by Castillo-Castañeda et al. found the highest incidence in the departments of Bolívar, Sucre, and Córdoba, while fewer cases were recorded in Tolima, Cundinamarca, Santander, Norte de Santander, and La Guajira.[15] These data demonstrate the distribution of the disease across the

Table 3. Frequency of systemic adverse effects (paraclinical evaluation)

Test/Procedure	Pre-treatment (A)	During treatment (B)	At the end of treatment (C)	McNemar p value	
	% (n)	% (n)	% (n)	A vs. B	A vs. C
Hematological abnormalities					
Leukocytes	19.8 (18)	27.5 (25)	20.9 (19)	0.265	1.000
Erythrocytes	69.2 (63)	39.6 (36)	54.9 (50)	0.152	0.024*
Hemoglobin	14.3 (13)	11.0 (10)	6.6 (6)	0.629	0.092
Hematocrit	5.5 (5)	3.3 (3)	2.2 (2)	0.727	0.453
Platelets	3.3 (3)	5.5 (5)	9.9 (9)	0.687	0.109
Other abnormalities					
ALT	4.4 (4)	48.4 (44)	39.6 (36)	< 0.001**	< 0.001**
AST	2.2 (2)	91.2 (83)	49.5 (45)	< 0.001**	< 0.001**
Alkaline phosphatase	13.2 (12)	23.1 (21)	8.8 (8)	0.078	0.289
Amylase	18.7 (17)	22.0 (20)	25.3 (23)	0.664	0.345
Creatinine	4.4 (4)	16.5 (15)	25.3 (23)	0.007**	< 0.001**
BUN	2.2 (2)	3.3 (3)	11.0 (10)	1.000	0.039*
Glycemia	64.8 (59)	53.8 (49)	57.1 (52)	0.089	0.281
Electrocardiogram	7.7 (7)	17.6 (16)	3.3 (3)	0.068	0.109

*< 0.005.
**< 0.001.

national territory and its concentration in areas where access to health services is limited, regions experiencing challenges in case finding and disease control, or places where cultural explanations of the event predominate, among other factors that underscore the importance of increasing studies on this disease.[16] In addition to the above, in the particular case of the population that was part of the study, the departments with the highest number of cases belong to a region of the country where illegal armed groups are concentrated, which leads to the presence of the military in the same area.[17]

In this population, ages ranged from 19 to 41 years; data on leishmaniasis in Colombia show a similar pattern to that reported in other countries in the Americas, where the most affected age group is between 20 and 50 years.[18] This pattern was also observed in international studies, where countries in the region have shown similar age distributions, with the disease concentrated among young adults.[19,20] The higher number of cases in young adults can be attributed to outdoor work and recreational activities, with greater exposure to vectors in endemic areas.[21] With the exception of gender (the study was conducted in a military population where the male population performs field patrol duties), the race and age in this study coincide with the information reported in other similar studies, where the mestizo population is the most affected by the disease.[21]

From a pharmacodynamic perspective, pentamidine exerts its antileishmanial effect by interfering with the synthesis of nucleic acids (DNA/RNA), proteins, and phospholipids in the parasite, inhibiting oxidative phosphorylation and preventing nucleotide incorporation.[22] In this study, the effectiveness of pentamidine isethionate was 100%, which is consistent with the findings of previous studies that reported a cure rate of 90%[23] or 96%[24] with comparable doses. However, it is important to note that the use of a lower than recommended dose can adversely impact the drug's efficacy, as evidenced by the study conducted by Robledo et al., where its effectiveness was 55.8%.[6] The results of this study demonstrate that pentamidine isethionate is a good choice for the management of CL; however, its administration under observation requires infrastructure and qualified human resources, aspects that could limit its use.

While pentamidine demonstrated a higher incidence of liver and kidney disorders at the conclusion of treatment, all cases were classified as mild. Liver abnormalities were the most common adverse effects, especially increased ALT and AST transaminases. This is consistent with other studies that found that a significant percentage of patients treated with pentamidine experienced elevated ALT levels, although these levels tended to normalize months after treatment.[7,25]

The study by Andersen et al. indicates a significant change in creatinine values,[7] and Gadelha et al. observed a slight increase in creatinine 1 week after treatment in all patients.[26] This finding aligns with the observed change in this parameter in the present study. However, there is a lack of documentation in the literature regarding the use of BUN values as an additional marker of renal status. The current study's findings

indicate substantial alterations in this parameter, suggesting that measuring it along with creatinine could enhance renal function assessment, facilitating differentiation between prerenal and intrarenal causes.

It is important to note that, despite its relatively rapid absorption, pentamidine is metabolized in the liver and has low urinary excretion. The organs with the highest accumulated concentrations are the kidney, liver, spleen, and adrenal glands, which explain the high frequency of alterations in liver function (ALT and AST) and kidney function (creatinine and BUN) observed in this study, as these are the main sites of accumulation and metabolism of the drug. This accumulation and slow release justify the need for close monitoring of these parameters;[22] these alterations may be the result of the pharmacokinetics of pentamidine. Kip et al.[27] have found that pentamidine absorbed in the liver may still be present 24 h after administration. The drug is metabolized by CYP450 enzymes, and low urinary excretion has been found. The organs with the highest accumulated concentrations of pentamidine are the kidneys, liver, spleen, and adrenal glands. These findings highlight the importance of improving the monitoring of patients, especially when the drug is administered under the usual conditions of healthcare in Colombia, where it may be given on an outpatient basis.

Conversely, no substantial alterations in hematological parameters were observed in this study. However, the technical data sheet for pentamidine isethionate recommends monitoring blood components during treatment, given that hematological effects may vary among patients, including the onset of leukopenia and thrombocytopenia.[22] Likewise, no significant changes in pancreatic function indicators or electrocardiographic alterations suggesting cardiovascular risk were observed. Nor were any changes in blood glucose levels recorded, which is consistent with previous studies such as that by Robledo et al., which indicate that cases of pentamidine-induced hypoglycemia are rare.[6] The low incidence of alterations in these parameters is also consistent with the findings of Oliveira et al.[28] This suggests that the variability in the manifestation of side effects is related to the clinical conditions of the patients, since certain effects may be less frequent in the absence of comorbidities or in individuals in good health.

The study has significant methodological strength as it is a retrospective cohort that used DOT by medical personnel, which positively impacts treatment adherence and allows for more accurate assessment of therapy performance. Some of the limitations of this study are attributable to the type of study, which may affect data quality (incomplete or outdated data, procedures not in line with management guidelines, and/or lack of contextual information); this was mainly evident in the lack of rigor in recording the description of the disease in patients. The lack of control over the variables of interest and the presence of biases (such as recall bias) were other limitations. Furthermore, the very specific population that was part of this study – military personnel (only men, mainly young) – prevents knowledge of the performance of pentamidine in other types of populations suffering from the disease. Another limitation of this study is that the identification of *Leishmania* was limited to the genus level; although species identification is not imperative to initiate treatment[12], having this information could facilitate the interpretation of the results and contribute to the understanding of local epidemiology, transmission patterns, and effectiveness of treatments.

The finding of 100% efficacy for pentamidine isethionate reinforces its position as a vital second-line treatment in accordance with international guidelines recommending it when pentavalent antimonials fail or are contraindicated.[12] Furthermore, this type of evidence is a valuable contribution to the management of neglected diseases such as leishmaniasis, for which research is lacking. While the safety profile is favorable, frequent alterations in analytes that account for renal and hepatic function were revealed, suggesting the need for improved medical monitoring. This is crucial for safe management, as treatment selection must carefully weigh efficacy against safety profiles and the logistical conditions of administration.

Conclusion

Pentamidine isethionate showed high efficacy with a favorable safety profile, although alterations in transaminases, BUN, and creatinine were common, suggesting the need for medical monitoring, especially in patients with liver or kidney problems, to detect complications and improve preventive strategies in endemic areas.

Acknowledgment

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Funding

The authors declare that this work was carried out with the authors' own resources.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The guidelines of the Declaration of Helsinki and Resolution 8430 of 1993 of the Colombian Ministry of Health were followed, according to which this research corresponds to a risk-free study since it is based on documentary data. In addition, the confidentiality of the participants' identification data was guaranteed, and only the healthcare team involved in the study had access to the information.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, informed consent was not required. The relevant recommendations have been followed.

Statement on the use of artificial intelligence. The authors declare that they did not use any type of generative artificial intelligence in the drafting of this manuscript.

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ORIGINAL ARTICLE

Real-world use, perception, satisfaction and adherence of calcipotriol and betamethasone dipropionate PAD-cream in patients with plaque psoriasis in Spain: cross-sectional online survey

Uso, percepción, satisfacción y adherencia en condiciones de vida real de una crema de calcipotriol y dipropionato de betametasona basada en la tecnología PAD en pacientes con psoriasis en placas en España: encuesta transversal online

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Abstract

Background: *A novel cream formulation, containing a fixed-dose combination of calcipotriol/betamethasone dipropionate (CAL/BDP) and based on the polyaphron dispersion (PAD) technology, was developed for a patient-friendly psoriasis management.* **Objective:** *To assess the use, perception, satisfaction and adherence to the CAL/BDP PAD-cream in a real-world setting among patients with plaque psoriasis in Spain.* **Material and methods:** *Online survey conducted originally in Germany and Spain through the company Wefight, between September and November 2023. Here we present individual data from the Spanish population. Demographic data, clinical disease characteristics and use, perception, satisfaction and adherence to CAL/BDP PAD-cream were analysed. Results were anonymized and underwent descriptive analysis.* **Results:** *The survey was completed by 86 current or past users of CAL/BDP PAD-cream for > 2 weeks in Spain (mean age 44.1 years, 65% females, mean psoriasis duration 12.5 years). The majority of patients (93%) were satisfied with CAL/BDP PAD-cream. Additionally, 92% preferred it to their previous topicals, and 70% reported high adherence (visual analogue scale 80-100). The 65% already noticed an improvement in their symptoms within 1 week.* **Conclusions:** *Patients with plaque psoriasis treated with CAL/BDP PAD-cream in the real-world setting in Spain show high satisfaction, good adherence and a positive perception of the product, suggesting that favourable results observed in clinical trials with CAL/BDP PAD-cream are reproduced in the clinical practice.*

Keywords: *Adherence. Calcipotriol/betamethasone dipropionate. Cream. Survey. Perception. Satisfaction.*

Resumen

Antecedentes: *Una nueva formulación en crema, que contiene una combinación a dosis fija de calcipotriol/dipropionato de betametasona (CAL/BDP) y basada en la tecnología de dispersión de poliafrones (PAD), fue desarrollada para un manejo cómodo de la psoriasis por parte del paciente.* **Objetivo:** *Evaluar el uso, la percepción, la satisfacción y la adherencia a CAL/*

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BDP PAD crema en condiciones de vida real en pacientes con psoriasis en placas en España. **Material y métodos:** *Encuesta online realizada en Alemania y España a través de la compañía Wefight, entre septiembre y noviembre de 2023. Se presentan los datos individuales de la población española. Se analizaron datos demográficos, características clínicas de la enfermedad y uso, percepción, satisfacción y adherencia a la CAL/BDP PAD crema. Los resultados fueron anonimizados y sometidos a un análisis descriptivo.* **Resultados:** *La encuesta fue completada por 86 usuarios actuales o previos de CAL/BDP PAD crema durante > 2 semanas en España (edad media 44.1 años, 65% mujeres, duración media de la psoriasis 12.5 años). La mayoría de pacientes (93%) estaban satisfechos con CAL/BDP PAD crema. Además, el 92% la prefirieron a sus tratamientos tópicos previos y el 70% reportaron una alta adherencia (escala visual analógica 80-100). El 65% ya notaron una mejoría en sus síntomas tras 1 semana de uso.* **Conclusiones:** *Los pacientes con psoriasis en placas tratados con CAL/BDP PAD crema en condiciones de vida real en España muestran alta satisfacción, buena adherencia y percepción positiva del producto, sugiriendo que los resultados favorables observados en los ensayos clínicos se reproducen en la práctica clínica.*

Palabras clave: *Adherencia. Calcipotriol/dipropionato de betametasona. Crema. Encuesta. Percepción. Satisfacción.*

Introduction

Psoriasis is a chronic immune-mediated skin disease affecting approximately 125 million people worldwide.[1] Between 1990 and 2019, approximately 2.99 million cases were diagnosed in Spain.[2] The comorbidity of psoriasis, together with the involvement of specific body areas, significantly impacts patients' quality of life, even in mild cases.[3]

Psoriasis can be classified as mild, moderate, or severe.[4] In mild cases, topical therapy is preferentially recommended.[5] Given that approximately 70% of patients with psoriasis in Spain present with a mild form,[6,7] topical therapies remain a fundamental pillar in disease management.[3]

Although different formulations and active ingredients exist for the topical treatment of psoriasis, certain unmet needs persist.[8] Adherence is recognised as a barrier to the success of topical therapies.[9] To improve adherence, it is crucial to enhance patient satisfaction with topical therapies.[10,11] Improvements in the vehicle may have a positive impact on both patient-reported outcomes and clinical outcomes.[12] Shared decision-making with patients and adapting vehicles to their preferences may mitigate non-adherence and treatment rejection.[13]

The fixed-dose combination of calcipotriol (CAL) and betamethasone dipropionate (BDP) is recommended as a first-line option for the topical treatment of psoriasis.[14] Recently, a new cream formulation has been developed using polyaphron dispersion (PAD) technology to provide a more convenient topical treatment for adults with plaque psoriasis affecting the body and scalp.[15] The CAL/BDP PAD cream vehicle demonstrates better sensory characteristics than foam and ointment, and is more manageable than oleogel.[16,17] In 2 phase III studies, CAL/BDP PAD cream showed safety and tolerability similar to CAL/BDP gel, while offering greater efficacy and convenience.[15,18] Through a matching-adjusted indirect comparison (MAIC), it was compared with CAL/BDP foam. Although efficacy was similar between both products, higher patient satisfaction was observed with CAL/BDP PAD cream.[19] These findings of greater satisfaction, as well as improved convenience of CAL/BDP PAD cream compared with CAL/BDP foam, were recently corroborated in a preference clinical trial between both formulations.[20] However, despite the high levels of acceptability and satisfaction observed with CAL/BDP PAD cream in clinical trials, there is limited evidence regarding patients' perceptions under real-world conditions.

A cross-sectional online survey conducted in Germany and Spain has, for the first time, reported results for CAL/BDP PAD cream in a real-world clinical practice setting in patients with plaque psoriasis. The pooled data from both countries suggest that the favourable outcomes observed under controlled clinical trial conditions are replicated in real-world clinical practice.[21] Given that a significant proportion of patients in this study were from Spain, it was considered relevant to perform a subanalysis of the Spanish population. The objective of this study was therefore to evaluate the use, perception, satisfaction, and adherence to CAL/BDP PAD cream under real-world conditions in patients with plaque psoriasis in Spain.

Method

Patient recruitment

This survey was conducted in Germany and Spain.[21] The present analysis reports only the results of patients recruited in Spain between September and November

2023 through the Wefight network. Current or previous users (within the last 3 months) of CAL/BDP PAD cream for more than 2 weeks with a diagnosis of psoriasis were included.

Survey design

By design, this study did not impact patient treatment. It consisted of a 10-minute electronic survey comprising 30 questions on demographic data, clinical disease characteristics, and the use, perception, satisfaction, and adherence to CAL/BDP PAD cream. The survey was conducted via Vik (the Wefight mobile application) and was also promoted on Wefight's social media platforms.

Statistical analysis

We conducted a descriptive analysis. No formal statistical hypotheses were planned, and no inferential statistical methods were applied.

Ethical aspects

Ethical principles and data protection standards were respected, as described in the section "Ethical considerations". All patients voluntarily agreed to participate in the survey and provided informed consent. As the study did not involve any type of intervention, approval from an ethics committee was not required.

Results

Demographic and clinical characteristics

A total of 86 Spanish patients with psoriasis participated in this survey. The demographic and clinical characteristics are presented in table 1.

Use of CAL/BDP PAD cream under real-world conditions in Spain

In Spain, 68 patients (79%) were current users of CAL/BDP PAD cream for more than 2 weeks, and 29 (34%) were previous users, having used the cream within the last 3 months for more than 2 weeks. Fifteen per cent of patients had used CAL/BDP PAD cream both currently and in the recent past.

CAL/BDP PAD cream was prescribed predominantly by dermatologists (72%), followed by primary care physicians (27%). In 36% of users, the initial prescription

Table 1. Demographic and clinical characteristics of patients who completed the survey in Spain

Characteristics	Respondents in Spain (n = 86)
Women, n (%)	56 (65.1%)
Age, mean (SD)	44.1 (13.8)
Age range, n (%)	
18-34 years	25 (29.1%)
35-44 years	25 (29.1%)
45-54 years	18 (20.9%)
55-64 years	10 (11.6%)
≥ 65 years	8 (9.3%)
Years since psoriasis diagnosis, mean (SD)	12.5 (11.8)
Type of psoriasis, n (%)	
Psoriasis	70 (81.4%)
Psoriasis + psoriatic arthritis	16 (18.6%)
Percentage of BSA affected by psoriasis, mean (SD)	10.8 (16.3)
BSA category, n (%)	
0-5%	51 (59.3%)
6-10%	15 (17.4%)
≥ 11%	20 (23.3%)
Number of affected body areas, mean (SD)	4.8 (3.1)
Affected body areas, n (%)	
Scalp	52 (60.5%)
Elbows	52 (60.5%)
Knees	34 (39.5%)
Hands	29 (33.7%)
Ears	25 (29.1%)
Feet	24 (27.9%)
Other areas of the legs	22 (25.6%)
Back	21 (24.4%)
Face	16 (18.6%)
Buttocks	13 (15.1%)
Neck	13 (15.1%)
Axillae	13 (15.1%)
Chest	13 (15.1%)
Other areas of the arms	13 (15.1%)
Fingernails	12 (14.0%)
Abdomen	12 (14.0%)
Genitals	11 (12.8%)
Navel	10 (11.6%)
Groin	10 (11.6%)
Toenails	9 (10.5%)
Gluteal cleft	5 (5.8%)
Impact of psoriasis on quality of life, n (%)	
Severe	32 (37.2%)
Moderate	41 (47.7%)
Mild	12 (14.0%)
None at all	1 (1.2%)
Previous psoriasis treatments*, n (%)	
Topical	49 (57.0%)
Oral	31 (36.0%)
Phototherapy or PUVA	23 (26.7%)
Injectable	19 (22.1%)
No treatment	10 (11.6%)
Other	3 (3.5%)

(Continues)

Table 1. Demographic and clinical characteristics of patients who completed the survey in Spain *(continued)*

Characteristics	Respondents in Spain (n = 86)
Current psoriasis treatments, n (%)*	
Topical	81 (94.2%)
Oral	26 (30.2%)
Injectable	19 (22.1%)
Phototherapy or PUVA	4 (4.7%)
Other	1 (1.2%)

*All respondents had selected "topical" as a current or previous treatment (current or past users of CAL/BDP PAD cream).
BSA: body surface area; SD: standard deviation; PUVA: psoralen plus ultraviolet A.

did not specify the number of weeks for which CAL/BDP PAD cream should be used. In 40% of cases, the prescription was renewed by the physician, whereas it was not renewed for 21% of patients.

Figure 1 shows the treatment patterns of CAL/BDP PAD cream in real-world clinical practice in Spain.

Satisfaction with CAL/BDP PAD cream in Spain

When patients were asked about their overall satisfaction with CAL/BDP PAD cream, 80 out of 86 respondents (93%) expressed satisfaction with the treatment. Of these, 48 (56%) reported being very satisfied and 32 (37%) indicated being somewhat satisfied. Only 6 patients (7%) reported being somewhat dissatisfied with CAL/BDP PAD cream, and none reported being very dissatisfied.

The mean time for patients to notice improvement in their psoriasis symptoms with CAL/BDP PAD cream was 8 days, although 65% of patients already reported improvement within 1 week (Fig. 2).

Perception of CAL/BDP PAD cream in Spain

Respondents rated different perception criteria related to their experience with CAL/BDP PAD cream on a scale from 0 ("strongly disagree") to 10 ("completely agree"). Figure 3 illustrates the percentage of patients who rated each criterion between 8 and 10. The 3 highest-rated criteria were that CAL/BDP PAD cream is "easy/convenient to apply", "well tolerated", and "does not cause itching/burning".

A total of 70% of patients (n = 60) reported that the use of CAL/BDP PAD cream had no effect or only a minimal impact on their daily activities and routine. Although 36% (n = 31) believed that CAL/BDP PAD cream might be noticeable to others, only 9 of them felt discriminated against or stigmatised.

Most respondents reported an improvement in self-esteem and a more positive perception of their appearance (Fig. 4A). Although challenges remain, such as difficulty wearing desired clothing and hairstyles (Fig. 4B), 69% of respondents felt that the benefits of CAL/BDP PAD cream outweighed the disadvantages, and 66% expressed willingness to use it again in the future (Fig. 4C). In addition, 92% of patients preferred CAL/BDP PAD cream over their previous topical therapy. Most also found that CAL/BDP PAD cream was easier to use (84%), associated with fewer side effects (80%), and more effective (74%) compared with their previous topical therapy (Fig. 5).

Among the 31 patients who used CAL/BDP PAD cream to treat the scalp, 23 (74%) reported that the cream was easy to apply and spread, and 19 (61%) found it easy to remove when washing their hair.

Adherence to CAL/BDP PAD cream in Spain

A total of 70% of patients achieved a score indicative of high adherence to CAL/BDP PAD cream on the visual analogue scale (VAS) (Fig. 6A). Responses to the 4-item Morisky Medication Adherence Scale (MMAS-4) revealed that 49% of patients sometimes discontinued CAL/BDP PAD cream when they felt better, and 45% reported having forgotten to use it at some point (Fig. 6B).

Discussion

This analysis focuses on data from the Spanish population of a previously published survey.[21] Of the 129 patients with plaque psoriasis who completed the survey in the pooled study, 86 (67%) belonged to the Wefight network in Spain. The demographic and clinical characteristics of the Spanish respondents were consistent with those reported in the original analysis,[21] as well as with those of patients who received CAL/BDP PAD cream in phase III trials.[18]

Most Spanish users of CAL/BDP PAD cream (93%) reported being satisfied with the product. This high level of satisfaction is consistent with the strong acceptability of the treatment previously demonstrated in phase III clinical trials, as assessed using the Psoriasis Treatment Convenience Scale (PTCS).[18] Such findings may be attributed to its formulation as an aqueous cream based on PAD technology.[22] The vehicle used

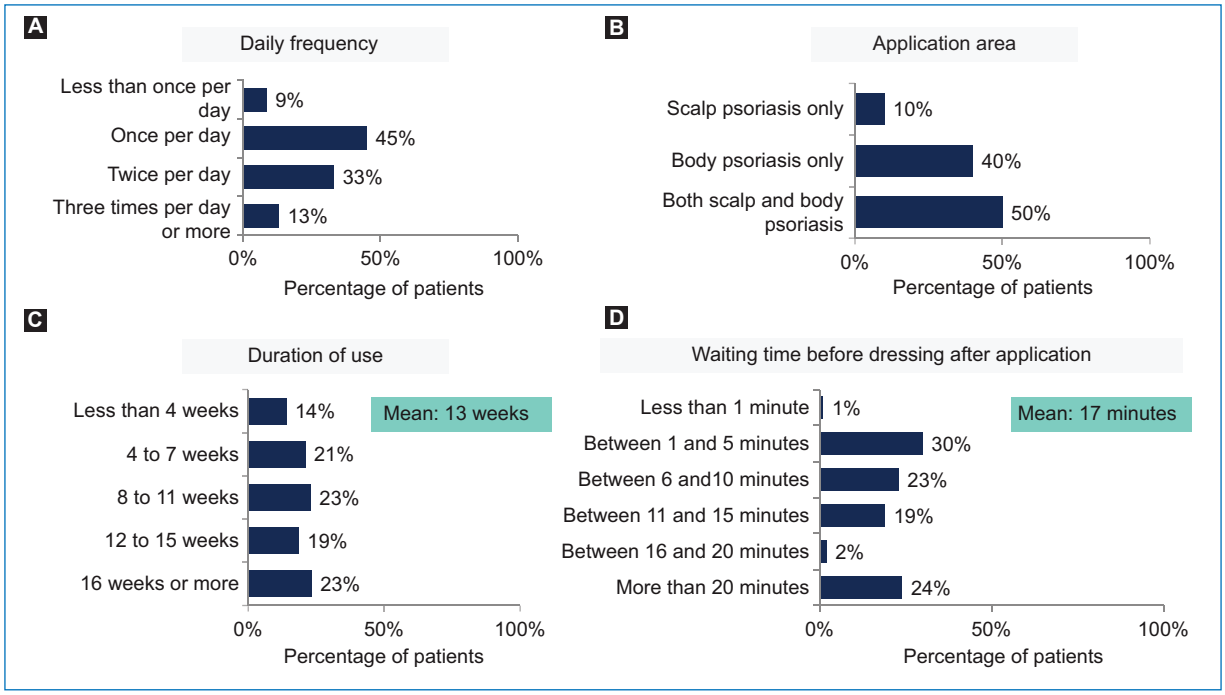

Figure 1. Real-world use of CAL/BDP PAD cream in Spain according to daily frequency **(A)**, application site **(B)**, duration of use **(C)**, and waiting time before dressing after application **(D)**. Percentages are rounded and calculated based on the total number of respondents in Spain (n = 86). BDP: betamethasone dipropionate; CAL: calcipotriol; PAD: polyaphron dispersion.

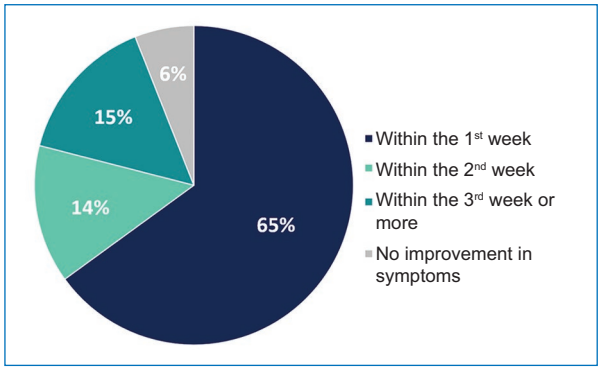

Figure 2. Percentage of patients who experienced improvement in psoriasis symptoms after different treatment durations with CAL/BDP PAD cream. Percentages are rounded and calculated based on the total number of respondents in Spain (n = 86). BDP: betamethasone dipropionate; CAL: calcipotriol; PAD: polyaphron dispersion.

has low greasiness, low stickiness, good spreadability, and adequate moisturising capacity.[17] These attributes, which align with patient preferences,[23] likely contribute to the positive perception of CAL/BDP PAD cream among the Spanish population and to their willingness to use it again in the future.

CAL/BDP PAD cream stands out when Spanish patients compare it with their previous experiences with topical therapies. Most prefer CAL/BDP PAD cream because it is more effective, has fewer side effects, and is easier to use. Previous studies have shown that CAL/BDP PAD cream generates greater satisfaction than other fixed-dose CAL/BDP formulations. Compared with CAL/BDP gel, the cream demonstrated a statistically significant improvement in quality of life and patient satisfaction, as evidenced by Dermatology Life Quality Index (DLQI), Subject Global Assessment (SGA), and treatment convenience outcomes.[24] In addition, an indirect comparison showed that patients considered the cream more convenient than the foam.[19] Kircik et al. confirmed this in a participant-blinded clinical trial, in which patients showed a preference for CAL/BDP PAD cream over CAL/BDP foam.[20]

Although adherence remains a challenge in the topical management of psoriasis,[25] in this survey 70% of Spanish patients reported high adherence to CAL/BDP PAD cream. This contrasts with former studies on other topical therapies, which also used a dichotomous

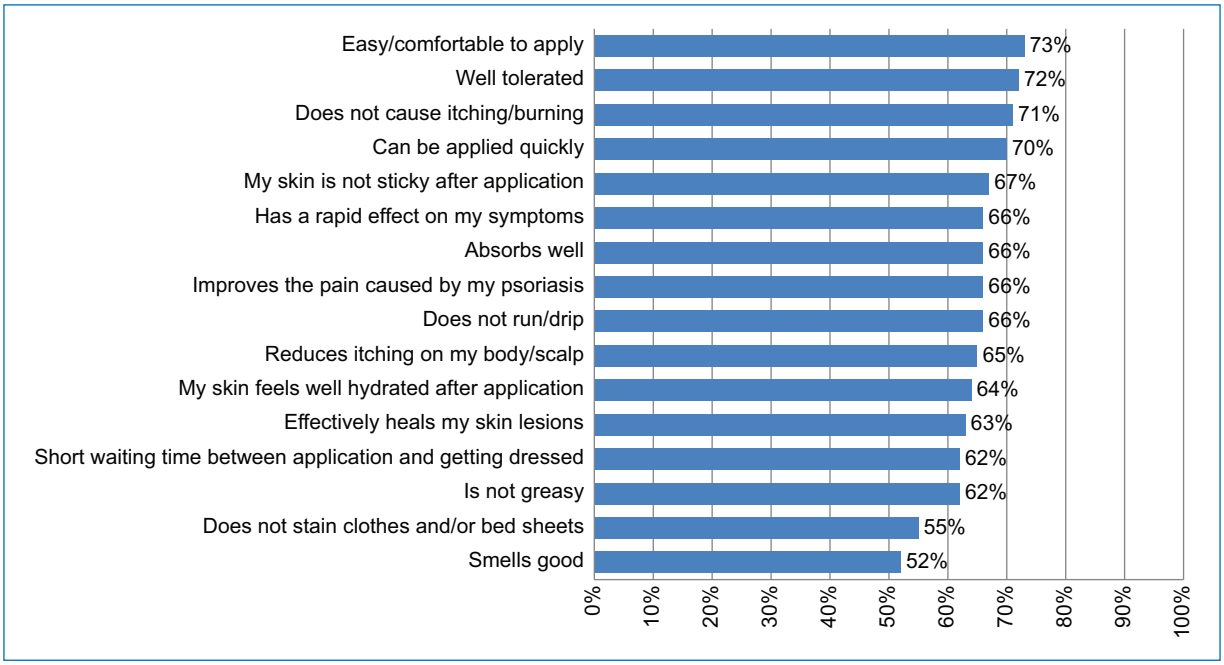

Figure 3. Percentage of patients expressing high or complete agreement with each perception criterion related to CAL/BDP PAD cream. Patients rated each criterion on a scale from 0 ("strongly disagree") to 10 ("completely agree"). The figure shows only the percentage of patients scoring each criterion between 8 and 10. Percentages are rounded and calculated based on the total number of respondents in Spain (n = 86). BDP: betamethasone dipropionate; CAL: calcipotriol; PAD: polyaphron dispersion.

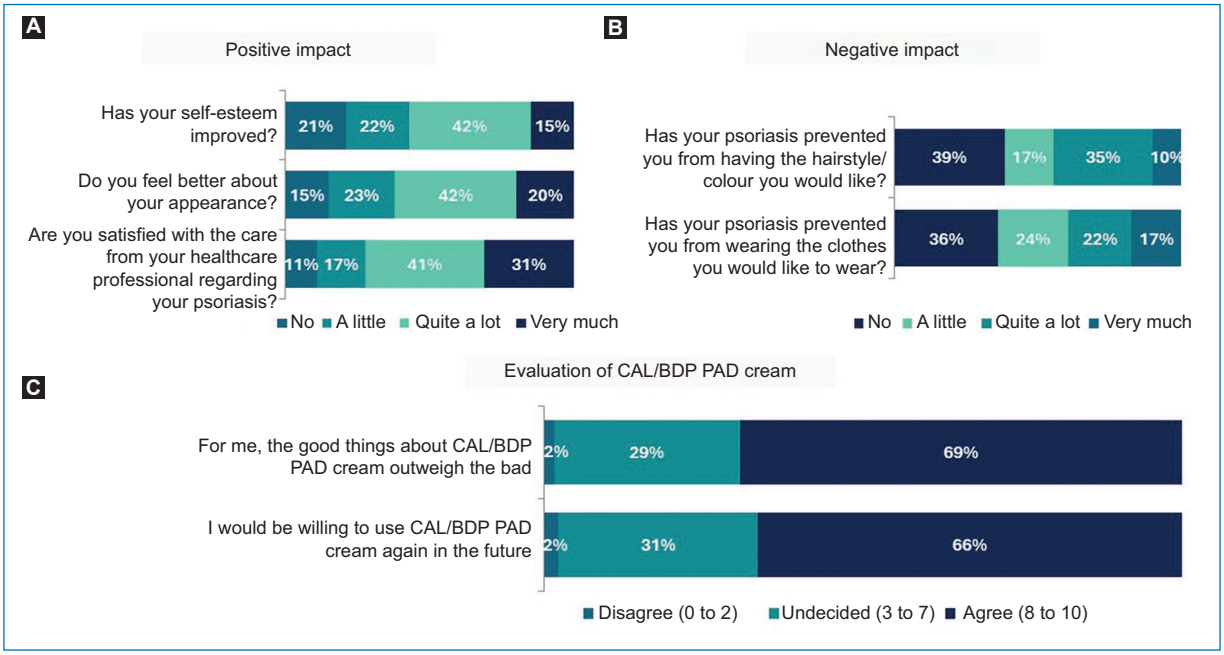

Figure 4. Positive impact **(A)**, negative impact **(B)**, and overall evaluation of CAL/BDP PAD cream **(C)** in a real-world clinical setting in Spain. Percentages are rounded and calculated based on the total number of respondents in Spain (n = 86). BDP: betamethasone dipropionate; CAL: calcipotriol; PAD: polyaphron dispersion; HCP: healthcare professional.

Figure 5. Comparison of CAL/BDP PAD cream with previously used topical therapies. "Agree" represents the total of positive responses ("agree" and "strongly agree"), and "disagree" represents the total of negative responses ("disagree" and "strongly disagree"). Percentages are rounded and calculated based on the total number of patients who had previously used topical treatment in Spain (n = 49). BDP: betamethasone dipropionate; CAL: calcipotriol; PAD: polyaphron dispersion.

classification of adherence and reported between 22% and 67% of adherent patients.[26] The high levels of treatment adherence observed with CAL/BDP PAD cream may be explained by the formulation attributes mentioned above, which led to a favourable perception of the product and high satisfaction. Greater treatment satisfaction positively influences adherence.[11]

The use of CAL/BDP PAD cream exceeded the recommended treatment duration (13 vs. 8 weeks). This may be attributed to the fact that 36% of users did not receive specific instructions regarding treatment duration in their prescriptions. Patients require personalised education on medication use to understand its correct application.[27] Our results are consistent with the consensus of an expert panel from the Psoriasis Group of the *Academia Española de Dermatología y Venereología (AEDV)*, which emphasised the need to improve communication between patients and healthcare professionals.[11]

The data from the Spanish population show some differences compared with the pooled analysis.[21] A higher proportion of CAL/BDP PAD cream prescriptions in Spain were issued by primary care physicians (27% vs. 22%).[21] Although both analyses showed a similar overall satisfaction rate (93% in both), a higher proportion of Spanish patients were very satisfied with the treatment (56% vs. 49%).[21] In addition, treatment adherence was also higher in the Spanish population (70% vs. 66%).[21] A lower proportion of Spanish patients reported that their daily activities and routines were affected by the use of CAL/BDP PAD cream (30% vs. 37%).[21] In Spain, patients rated all perception criteria more favourably in relation to CAL/BDP PAD cream. Among patients who used CAL/BDP PAD

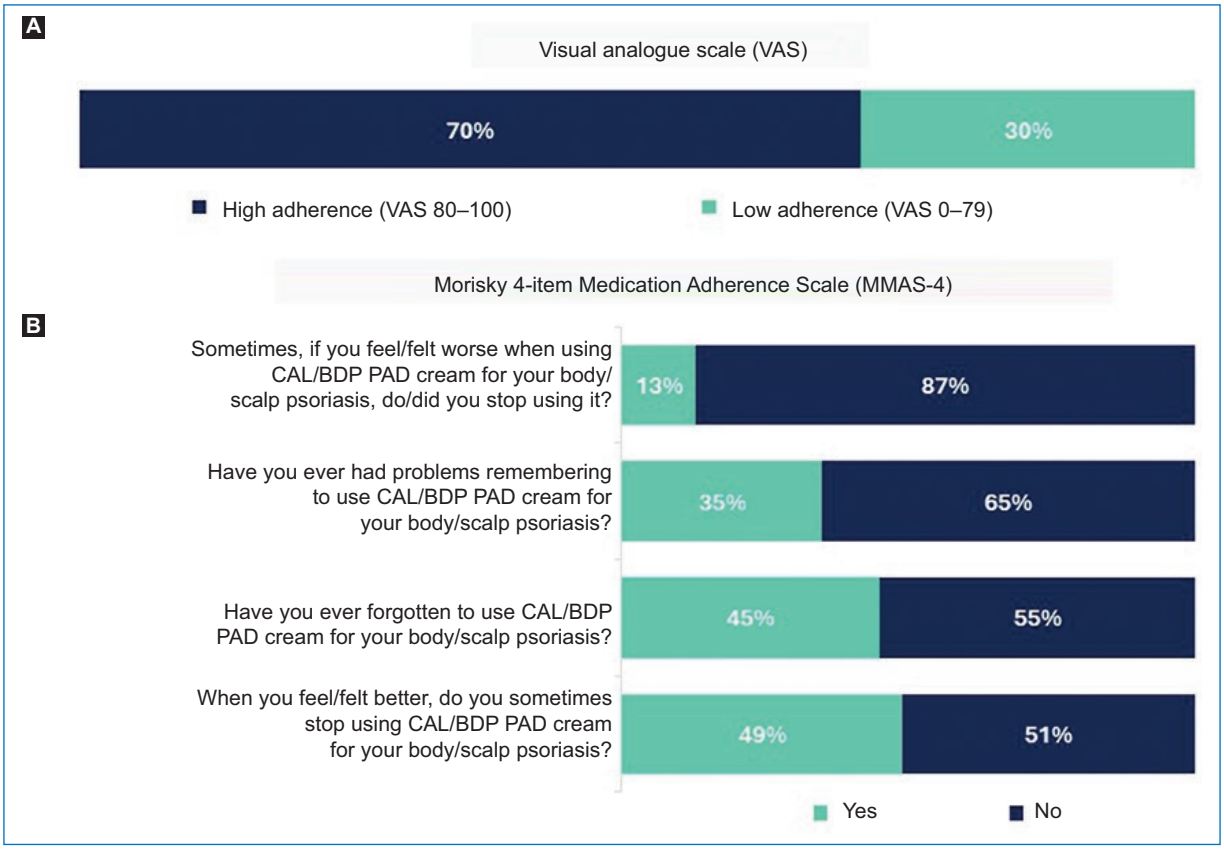

Figure 6. Adherence to CAL/BDP PAD cream assessed using the visual analogue scale (VAS) **(A)** and the 4-item Morisky Medication Adherence Scale (MMAS-4) **(B)**. Percentages are rounded and calculated based on the total number of respondents in Spain (n = 86). BDP: betamethasone dipropionate; CAL: calcipotriol; VAS: visual analogue scale; MMAS-4: 4-item Morisky Medication Adherence Scale; PAD: polyaphron dispersion.

cream to treat the scalp, perception was also more positive. Spanish patients considered it easier to apply (74% vs. 65%) and easier to remove when washing the hair (61% vs. 52%).[21] The differences compared with the pooled analysis suggest that the German population may consist of patients with lower adherence and a less favourable evaluation of the product, which may indicate that populations from different countries prioritise different aspects of treatment. Cultural differences may therefore influence patients' levels of perception and satisfaction when evaluating the product.

This article presents the results of a survey on the use and perceptions of CAL/BDP PAD cream in a real-world setting in Spain. The strengths and limitations of this research correspond to those described in the original analysis.[21] The inclusion of patients who had used CAL/BDP PAD cream for more than 2 weeks ensured that respondents were sufficiently familiar with the product. Respondents were members of Wefight, a well-established psoriasis patient network in Europe. However, this study has certain limitations. On the one hand, including patients from other national sources could have improved the generalisability of our findings to the Spanish population with plaque psoriasis. On the other hand, there are also limitations related to the nature of the study and the survey design. Voluntary participation in online surveys may introduce selection bias.[28] Furthermore, self-administered surveys may produce results that differ from those obtained via telephone or face-to-face interviews. Since our results were entirely patient-reported, disease characteristics may be less reliable compared with data reported by healthcare professionals. However, adherence and treatment patterns may better reflect real-world clinical practice, as patients may feel less influenced in the absence of an interviewer.[29,30]

Conclusions

Patients with plaque psoriasis treated with CAL/BDP PAD cream for more than 2 weeks in Spain showed

high satisfaction with the treatment and good adherence, suggesting that the favourable results observed in clinical trials are reproduced in real-world clinical practice in Spain. CAL/BDP PAD cream was well perceived by Spanish users, especially among those who used it to treat the scalp. The small differences vs the pooled analysis highlight the importance of considering patient preferences when prescribing topical therapies, as patients from different countries may prioritise different aspects of treatment. Good communication between patients and healthcare professionals is essential in psoriasis management to ensure that prescribed products meet expectations. However, although the results are favourable, conclusions should be interpreted with caution due to limitations inherent to the study design, including potential selection bias and the small sample size.

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Conflicts of interest

The authors declare that J.L. López-Estebaranz has acted as a consultant, participated in clinical trials, and received speaker fees from Almirall, Janssen, Leo Pharma, Lilly, AbbVie, Bioderma, Galderma, UCB, Novartis, Pierre Fabre, Invasix, Isdin, and Incyte. E. García-Zamora has received fees from Almirall for lectures and presentations. J. Griffiths and M. Menéndez declare no conflicts of interest. J. Galván is an employee of Almirall.

Ethical considerations

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

Confidentiality, informed consent, and ethical approval. The authors obtained individual informed consent for the analysis of data collected through a non-interventional and anonymised survey. Due to the nature of the study, ethics committee approval was not required. Appropriate ethical recommendations were followed.

Statement on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or content creation of this manuscript.

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REVIEW ARTICLE

Use of botulinum toxin type A in nonconventional regions of the mid and lower face, and neck: a systematic review of clinical trials

Uso de toxina botulínica tipo A en regiones no convencionales de los tercios medio e inferior faciales y el cuello: revisión sistemática de ensayos clínicos

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Abstract

Botulinum toxin type A (BoNT-A) has expanded its indications beyond the upper facial third toward less conventional anatomical regions of the mid and lower face and neck, including the mandibular, cervical, and nasal areas, with both aesthetic and functional objectives. However, the available evidence remains scattered and demonstrates considerable variability regarding injection techniques, dosing protocols, and evaluated outcomes. The aim of this systematic review was to evaluate the efficacy and safety of BoNT-A use in these regions through a critical analysis of the literature. A systematic search was conducted in biomedical databases, including clinical trials assessing the application of botulinum toxin in nontraditional areas of the mid and lower face and neck. A total of 18 studies involving 2106 participants were included. Variables analyzed included clinical indications, administered doses, injection techniques, duration of therapeutic effect, and adverse events. The results demonstrated clinically significant improvement across several aesthetic and functional indications, particularly reduction of masseter volume, improvement of platysmal bands, and control of nasal symptoms. Reported adverse events were predominantly mild and transient. In conclusion, BoNT-A represents an effective and safe therapeutic alternative for the treatment of less conventional regions of the face and neck. Nevertheless, the heterogeneity identified highlights the need for standardized protocols and studies with greater methodological rigor and long-term follow-up.

Keywords: *Botulinum toxin type A. Mandible. Neck. Nose. Randomized controlled trial.*

Resumen

La toxina botulínica tipo A (BoNT-A) ha expandido sus indicaciones más allá del tercio superior facial hacia regiones anatómicas menos convencionales de los tercios medio e inferior faciales y el cuello, incluyendo las áreas mandibular, cervical y nasal, con aplicaciones con objetivos tanto estéticos como funcionales. No obstante, la evidencia disponible se encuentra dispersa y presenta una notable variabilidad en cuanto a técnicas de aplicación, dosificación y desenlaces evaluados. El objetivo de esta revisión sistemática fue evaluar la eficacia y la seguridad del uso de BoNT-A en estas regiones mediante un análisis crítico de la literatura. Se realizó una búsqueda sistemática en bases de datos biomédicas, incluyendo ensayos clínicos que evaluaran la aplicación de BoNT-A en áreas no tradicionales de los tercios medio e inferior faciales y el cuello. Se incluyeron 18 estudios con un total de 2106 participantes. Se analizaron variables como indicaciones clínicas,

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dosis empleadas, técnicas de administración, duración del efecto terapéutico y eventos adversos. Los resultados evidenciaron una mejoría clínicamente significativa en diversas indicaciones estéticas y funcionales, destacando la reducción del volumen masetérico, la mejoría de las bandas platismales y el control de síntomas nasales. Los eventos adversos reportados fueron predominantemente leves y transitorios. En conclusión, la BoNT-A representa una alternativa terapéutica eficaz y segura para el tratamiento de regiones menos convencionales de la cara y el cuello. Sin embargo, la heterogeneidad identificada subraya la necesidad de desarrollar protocolos estandarizados y de realizar estudios con mayor rigor metodológico y seguimiento a largo plazo.

Palabras clave: *Toxina botulínica tipo A. Mandíbula. Cuello. Nariz. Ensayo clínico aleatorizado.*

Introduction

Botulinum toxin type A (BoNT-A) acts by blocking acetylcholine release at the neuromuscular junction, producing reversible muscle relaxation that has supported its use in neuromuscular disorders and aesthetic applications since the late 20th century. Traditionally, its best-established indications have included the treatment of dynamic wrinkles of the upper third of the face, hemifacial spasm, and certain focal dystonias. However, over the past 2 decades, its application has expanded to less conventional anatomical regions of the middle and lower thirds of the face, neck, and nose for both aesthetic and therapeutic purposes. This expansion is based on the ability of localized neuromuscular modulation to modify facial contour, masticatory dynamics, and nasal physiology. Nevertheless, the available evidence is heterogeneous in terms of study design, sample size, and outcomes, thus warranting a systematic synthesis.[1-4]

In the cervical region, injection into the platysma muscle for the treatment of platysmal bands and redefinition of the cervicomandibular angle has shown favorable results in controlled studies, providing a minimally invasive alternative for patients with moderate platysmal prominence.[3] However, the anatomical complexity of this region requires technical precision to minimize adverse events. Accordingly, recent studies have emphasized protocols based on anatomical landmarks, units per injection point, and strict patient-selection criteria to optimize efficacy and safety.[2,5,6] In the mandibular region, injection into the masseter muscle has emerged both as a cosmetic procedure for facial contour reduction and as a therapeutic intervention for masseter hypertrophy, bruxism, and myofascial pain.[4] Clinical trials have reported consistent reductions in muscle volume and symptomatic improvement over the short and medium term.[2,4]

Nasal applications represent another area of interest because of their dual functional and aesthetic purposes. Intranasal administration of BoNT-A has been investigated for the management of rhinorrhea and congestion in chronic rhinitis through inhibition of glandular cholinergic innervation,[7] whereas, for aesthetic purposes, it has been used to modify specific nasal features in selected patients.

In this context, the present systematic review aims to provide a critical and comparative synthesis of the available evidence on the use of BoNT-A in nonconventional regions of the middle and lower thirds of the face and the neck, with specific emphasis on the neck, mandible, and nose. Unlike previous reviews focused on isolated applications or observational studies, this review exclusively integrates clinical trials and comparatively analyzes variables such as dose, injection sites, formulations used, duration of the therapeutic effect, and safety profile according to the anatomical region treated.[1-4,6-8]

The objective of this review was to determine whether current evidence supports the safe and effective use of BoNT-A in these areas and whether consistent technical patterns exist that could guide more standardized clinical protocols. We hypothesized that, although the available studies show favorable aesthetic and therapeutic outcomes, methodological and technical heterogeneity limits comparability between studies and hinders the formulation of universal clinical recommendations.[2-10]

Methods

We conducted this systematic review in accordance with the recommendations of the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to identify, analyze, and synthesize evidence exclusively from randomized controlled clinical trials evaluating the use of BoNT-A in less commonly treated anatomical areas of the middle and lower thirds of the face and the neck. For this purpose, a systematic literature search was conducted in biomedical databases to identify relevant studies.

This systematic review was not registered in PROSPERO because the methodological protocol was developed for institutional academic purposes before formal publication was considered. Nevertheless, the search, selection, and analysis methods were defined a priori, and the PRISMA recommendations for conducting and reporting systematic reviews were followed.

The selection criteria were established using a structured approach. Only randomized clinical trials comparing BoNT-A administration with placebo, no treatment, or another active intervention were included.[11-15] Eligible participants were adults who had received BoNT-A in any of the abovementioned areas, without restrictions regarding sex, race, or clinical diagnosis, provided that the purpose of the procedure was aesthetic or functional. All commercially available BoNT-A formulations were considered eligible, without restrictions on dose, number of injection sites, or technique used.[16-18]

The literature search was conducted in PubMed/MEDLINE, Embase, and LILACS between September 29, 2025, and December 15, 2025. Priority was given to studies published during the previous 10 years; however, a clinical trial published approximately 30 years earlier was included because of its clinical relevance and the limited evidence available on the application of BoNT-A in the nasal region. MeSH terms, Emtree terms, and free-text terms related to BoNT-A and the anatomical regions of interest were used. The search strategy combined the Boolean operators AND and OR and included the terms "Botulinum Toxins," "Botulinum Toxins, Type A," "masseter," "mandible," "platysma," "neck," "nose," and "rhinitis," together with filters for randomized clinical trials. Only studies published in English or Spanish were included.

Study selection was conducted in 2 phases. In the first phase, titles and abstracts were screened to exclude records that did not meet the inclusion criteria. In the second phase, the full texts of potentially eligible studies were reviewed. This process was conducted independently by 2 reviewers, who resolved disagreements by consensus or through the involvement of a third reviewer.

The risk of bias in the included trials was assessed using the Risk of Bias 2 tool (RoB 2), which is specifically designed for randomized clinical trials.[19] This tool enabled the assessment of 5 domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported results. Each domain was rated as having a low risk of bias, some concerns, or a high risk of bias. The assessment was conducted independently by 2 reviewers, and disagreements were resolved by consensus. The assessment results were presented in descriptive tables and summary plots that enabled visualization of the distribution of risk of bias across the studies.

Data extraction was performed using a standardized form designed to collect the relevant variables from each study. The main characteristics of the included trials are described in table 1.[12-18,20-30] Data were extracted by 1 reviewer and independently verified by a 2nd investigator to ensure consistency and accuracy. No formal assessment of the certainty of the evidence using the GRADE system was conducted because of the substantial clinical and methodological heterogeneity among the included trials, particularly regarding the doses used, administration techniques, assessment scales, and reported outcomes. This heterogeneity limited study comparability and the feasibility of conducting a homogeneous quantitative synthesis.

A narrative synthesis organized by anatomical region – neck,[17,20-22] mandible,[11-15,23,24] and nose[25] – was prepared, and the observed effects were described in terms of safety and efficacy. Interpretation of the evidence was based on the direction of the effect, the magnitude of the reported differences, and consistency across studies. The information was presented in summary tables detailing the main characteristics and most relevant findings of each trial.[17,20-25]

Because this was a systematic review of the literature, approval by an ethics committee and informed consent were not required.

Results

Study selection

A total of 610 records were identified. After the removal of 206 ineligible records, 404 titles and abstracts were assessed, of which 349 were excluded. Retrieval of the full text was attempted for 55 articles, but 18 could not be obtained. After the full-text assessment of 37 articles, 19 were excluded because they did not meet the eligibility criteria. Finally, 18 randomized clinical trials were included in the review (Fig. 1).

General characteristics

The 18 randomized clinical trials included in the review, summarized in tables 1 and 2, enrolled a total of 2106 participants treated with BoNT-A in the neck, mandible, or nose.[12-18,20-30] Most studies were double-blind, placebo-controlled trials conducted in adult populations, predominantly comprising women. Doses

Table 1. Characteristics of the included studies

Authors, year of publication	Population	Intervention	Comparator
Park et al.[12], 2022	(n = 30); masseter hypertrophy	BoNT-A 25 U/masseter + nocturnal oral appliance	BoNT-A alone
Lee et al.[13], 2015	(n = 20); masseter hypertrophy; mean age, 28.5 years	BoNT-A 25 U/masseter; second dose at 4 months (group II)	Single-session BoNT-A
Lee et al.[14], 2024	(n = 80); benign masseter hypertrophy	Botulax 24-96 U (3 injection sites/masseter)	Placebo
Bae et al.[15], 2020	(n = 40); post-thyroidectomy	BoNT-A 50 U administered intraoperatively into the platysma	Placebo
Liew et al.[16], 2024	(n = 187); grade 4-5 masseter hypertrophy	OnabotA 24-96 U (3 injection sites/ masseter)	Placebo
Wei et al.[17], 2015	(n = 98); bilateral masseter hypertrophy	BoNT-A 35 U/masseter + masticatory exercises	BoNT-A without exercise
Seok et al.[18], 2024	(n = 180); bilateral masseter hypertrophy	PrabotulinumtoxinA 48 U (24 U/masseter)	Placebo
Fabi et al.[20], 2025	(n = 408); moderate-to-severe platysmal prominence; mean age, 49.7 years	OnabotA 26-36 U in the neck and jawline	Placebo
Rohrich et al.[21], 2025	(n = 171); platysmal prominence; mean age, 50 years	OnabotA 26-72 U in the submandibular platysma	Placebo
Shridharani et al.[22], 2025	(n = 381); grade 3-4 platysmal prominence; mean age, 48 years	OnabotA 26-36 U in the superficial platysma	Placebo (NS)
De la Torre Canales et al.[23], 2022	(n = 80); persistent myofascial pain; 100% women	BoNT-A (10-25 U into the temporalis + 30-75 U into the masseter)	Placebo
De la Torre Canales et al.[24], 2024	(n = 32); refractory myofascial pain; mean age, 43 years; 84% women	BoNT-A 80 U total (masseter + temporalis)	Placebo (NS)
Kim et al.[25], 1998	(n = 60); intrinsic rhinitis; mean age, 43 years	BoNT-A 4 U/nostril (middle and inferior turbinates) under endoscopic guidance	Placebo (0.9% NS)
Carruthers et al.[26], 2025	(n = 187); masseter hypertrophy (MMPS grade 4-5)	OnabotA 24-96 U bilaterally (3 injections/ masseter)	Placebo
Ayala et al.[27], 2024	(n = 40); muscular TMD (DC/TMD)	BoNT-A 80 U (masseter + temporalis)	Placebo
Jeong et al.[28], 2024	(n = 30); after facial fracture	BoNT-A 15-30 U into the superficial parotid gland under US guidance	Placebo
Shabaan et al.[29], 2025	(n = 42); masseter myofascial pain; mean age, 34.8 years	BoNT-A 100 U (US-guided intraoral injection)	BoNT-A administered extraorally under US guidance
Graciani et al.[30], 2025	(n = 40); idiopathic cervical dystonia	AbobotulinumA 417 U under US guidance	AbobotulinumA under EMG guidance

BoNT-A: botulinum toxin type A; DC/TMD: Diagnostic Criteria for Temporomandibular Disorders; EMG: electromyography; MMPS: Masseter Muscle Prominence Scale; NS: normal saline; TMD: temporomandibular disorders; US: ultrasound.

and techniques varied according to whether the indication was aesthetic or functional.

Neck

Three phase III clinical trials demonstrated a significant improvement in moderate-to-severe platysmal bands compared with placebo, using doses ranging from 26 to 72 U and with a mean duration of effect of 12-16 weeks.[20-22]

In the postoperative setting, intraoperative injection of the platysma reduced pain and improved scar quality.[15]

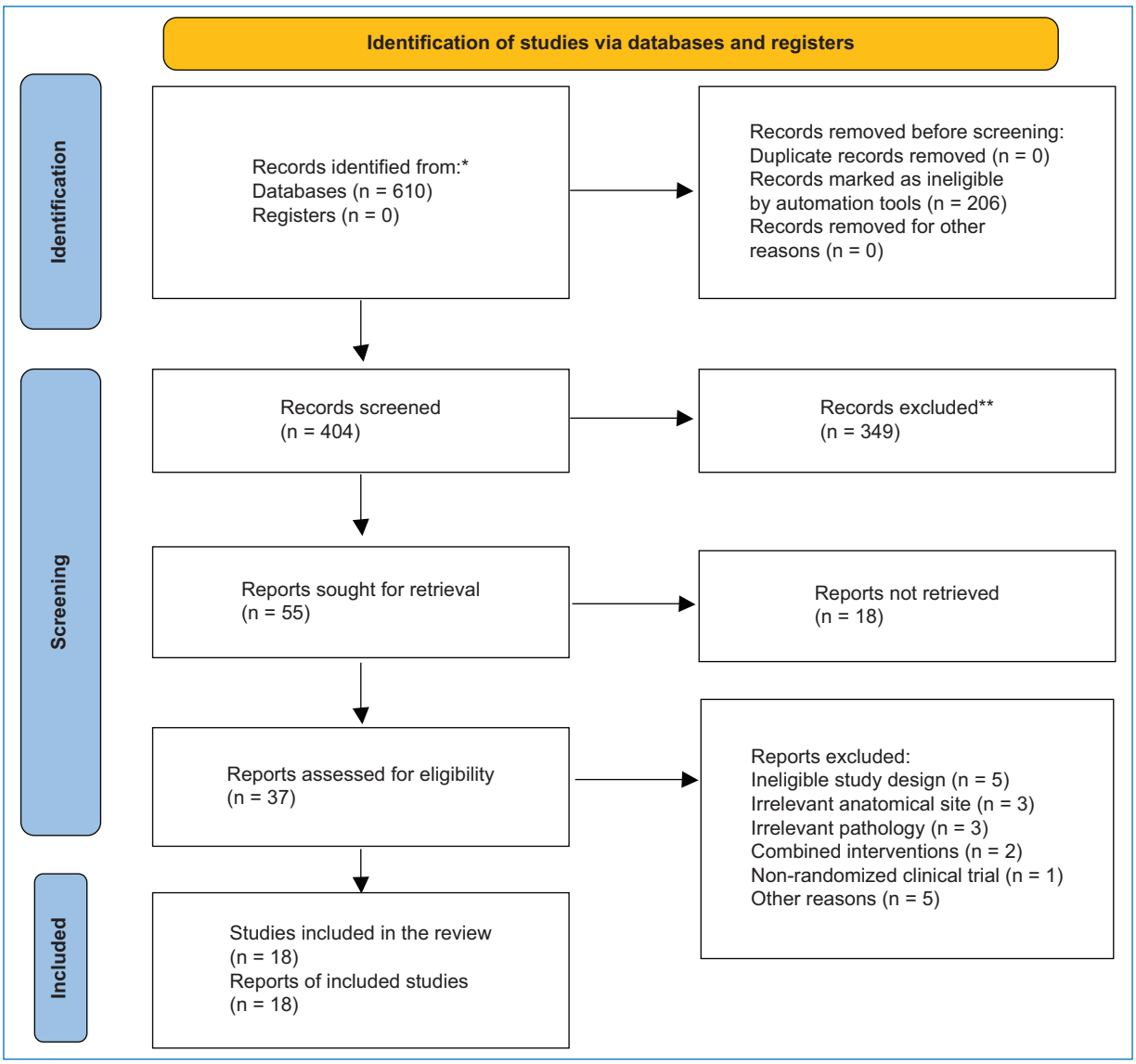

Figure 1. PRISMA flow diagram of the study selection process.

In cervical dystonia, a randomized clinical trial showed that ultrasound guidance had efficacy comparable to electromyographic guidance for BoNT-A administration, with no serious adverse events.[30]

Mandible and masticatory region

Most studies addressed bruxism, myofascial pain, and masseter hypertrophy. In the latter, phase II-III trials demonstrated a significant reduction in muscle volume and objective aesthetic improvement, with a dose-dependent effect and an approximate duration of 3-9 months; retreatment at approximately 6 months was required in some cases.[14,16,18,26]

Similarly, a randomized clinical trial evaluated BoNT-A injection into the parotid gland and demonstrated a significant reduction in gland volume and improvement in lower facial contour, thereby broadening the aesthetic applications of BoNT-A in the mandibular region.[28]

In myofascial pain and temporomandibular disorders, 4 randomized clinical trials found significant reductions in pain assessed using a visual analogue scale, as well as functional improvement, compared with placebo.[23,24,27,29] The use of ultrasound guidance improved the precision and safety of the procedure.

The reported adverse events were mild and transient, mainly partial masticatory weakness and local pain at the injection site.

Table 2. Clinical results and main outcomes of the included studies

Authors, year of publication	Intervention	Comparator	Outcomes	Results
Park et al.[12], 2022	BoNT-A 25 U/masseter	BoNT-A alone	Facial volume, mandibular contour	Significant reduction at 24 weeks ($p = 0.046$), greater with BoNT-A alone
Lee et al.[13], 2015	BoNT-A 25 U/masseter; second dose at 4 months (group II)	Single-session BoNT-A	Facial volume, muscle thickness	Greater reduction with 2 sessions (–24,072 mm ≥ and –3.8 mm; $p < 0.001$)
Lee et al.[14], 2024	BoNT-A (Botulax) 24-96 U (3 injection sites/masseter)	Placebo	Masseter thickness, lower-third facial volume, satisfaction, investigator assessment, adverse events	MMT reduction of –2.33 to –3.79 mm according to dose; satisfaction, 50-69%; ≥ 50% improvement, 60-81%; no serious adverse events
Bae et al.[15], 2020	BoNT-A 50 U administered intraoperatively into the platysma	Placebo	Scar appearance (SBSES, MSS)	Significant improvement at 24 weeks ($p \leq 0.03$)
Liew et al.[16], 2024	OnabotA 24-96 U (3 injection sites/masseter)	Placebo	Facial width, mandibular angle	Reduction in facial width (–4.7 to –5.6 mm; $p < 0.001$); 4° increase in mandibular angle; high satisfaction
Wei et al.[17], 2015	BoNT-A 35 U/ masseter + masticatory exercises	BoNT-A without exercise	Rehypertrophy, duration of effect, satisfaction	Less rehypertrophy ($p < 0.01$), prolonged effect (12 months), and 97% satisfaction
Seok et al.[18], 2024	BoNT-A (prabotulinumtoxinA) 48 U (24 U/masseter)	Placebo	Masseter thickness, duration of effect	Reduction of 2.9 mm at 12 weeks ($p < 0.0001$); effect lasting up to 6 months
Fabi et al.[20], 2025	BoNT-A (onabotulinumtoxinA) 26-36 U in the neck and jawline	Placebo	Cervical band scale, satisfaction	≥ 2-grade improvement: 32% vs. 1.9% ($p < 0.0001$); satisfaction: 66% vs. 11%
Rohrich et al.[21], 2025	BoNT-A (onabotulinumtoxinA) 26-72 U in the submandibular platysma	Placebo	Aesthetic improvement of the neck (C-APPS), safety	≥ 1-grade improvement: 77-88% vs. 12% ($p < 0.0001$); mild dysphagia in 3.7% with high doses
Shridharani et al.[22], 2025	BoNT-A (onabotulinumtoxinA) 26-36 U in the superficial platysma	Placebo (NS)	Grade of cervical bands	≥ 2-grade improvement: 41% vs. 2% ($p < 0.0001$); effect maintained for 120 days
De la Torre Canales et al.[23], 2022	BoNT-A (10-25 U into the temporalis + 30-75 U into the masseter)	Placebo	Pain, mouth opening, lateral mobility	Greater mouth opening and lateral mobility; pain reduction ($p < 0.05$); no differences according to dose
De la Torre Canales et al.[24], 2024	BoNT-A 80 U total (masseter + temporalis)	Placebo (NS)	Pain (VAS), pain modulation, quality of life	Pain decreased from 76 to 28 vs. 70 to 56 with placebo; ≥ 50% pain relief: 68.8% vs. 6.3% ($p < 0.001$); improvements in pain modulation and quality of life
Kim et al.[25], 1998	BoNT-A 4 U/nostril administered into the middle and inferior turbinates under endoscopic guidance	Placebo (0.9% NS)	Rhinorrhea, tissue use, congestion, sneezing	Significant reduction in rhinorrhea (–43%; $p < 0.05$) and tissue use (–54%; $p < 0.05$); no differences in congestion or sneezing
Carruthers et al.[26], 2025	BoNT-A (onabotulinumtoxinA) 24-96 U bilaterally (3 injections/masseter)	Placebo	Facial volume, mandibular contour	Reduction in facial volume (–5 to –8 cm^3; $p < 0.001$); effect lasting 4-6 months
Ayala et al.[27], 2024	BoNT-A 80 U (masseter + temporalis)	Placebo	Pain (VAS), condylar displacement	Pain decreased from 6.4 to 1.0 vs. 6.1 to 4.5 ($p < 0.001$); no functional impairment

(Continues)

Table 2. Clinical results and main outcomes of the included studies *(continued)*

Authors, year of publication	Intervention	Comparator	Outcomes	Results
Jeong et al.[28], 2024	BoNT-A 15-30 U into the superficial parotid gland under US guidance	Placebo	Parotid volume, xerostomia	Reduction in parotid volume (–11% to – 15%; p < 0.0001); no xerostomia
Shabaan et al.[29], 2025	BoNT-A 100 U (US-guided intraoral injection)	Extraoral BoNT-A injection under US guidance	Pain (VAS), MMO, quality of life	Lower pain scores (1.9 vs. 4.6; p = 0.008); MMO opening and better quality of life with the intraoral approach for up to 3 months
Graciani et al.[30], 2025	BoNT-A (abobotulinumtoxinA) 417 U under US guidance	AbobotulinumtoxinA under EMG guidance	Total TWSTRS score and subscales, > 30% reduction, TWSTRS score < 20, adverse events	TWSTRS reduction: –23.5% with US vs. –21.5% with EMG; > 30% reduction: 30% in both groups; TWSTRS score < 20: 25% with US vs. 20% with EMG; no significant adverse events

BoNT-A: botulinum toxin type A; C-APPS: Clinician Allergan Platysma Prominence Scale; EMG: electromyography; MMO: maximum mouth opening; MMPS: Masseter Muscle Prominence Scale; MMT: masseter muscle thickness; MSS: Manchester Scar Scale; SBSES: Stony Brook Scar Evaluation Scale; NS: normal saline; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; US: ultrasound; VAS: visual analogue scale.

Nose

A randomized clinical trial showed a significant reduction in rhinorrhea among patients with intrinsic rhinitis during the first few weeks after intranasal BoNT-A injection, with no relevant changes in nasal congestion. The effect gradually diminished between weeks 8 and 24, and no serious adverse events were reported.[25]

Technical characteristics of administration, clinical outcomes, and safety

Table 3 illustrates the technical characteristics and clinical outcomes of BoNT-A administration according to the anatomical region and therapeutic or aesthetic indication. For lower facial contouring and masseter hypertrophy, deep intramuscular injections into the masseter muscle were the most frequently used technique, with bilateral doses ranging from 24 to 96 U distributed across 3 injection sites per side. These treatments achieved significant reductions in facial volume and sustained aesthetic improvement for 4-6 months.[13,14,16,26]

For temporomandibular disorders and myofascial pain, total doses ranging from 80 to 100 U were used for bilateral injections into the masseter and temporalis muscles, distributed across multiple trigger points, with follow-up of up to 6 months. Significant pain reduction and improvement in mandibular function were observed.[23,24,27,29]

For cervical rejuvenation and the treatment of platysmal bands, superficial injection techniques targeting the platysma and jawline used between 26 and 72 U of BoNT-A, resulting in aesthetic improvement and high patient satisfaction, although there was an occasional risk of dysphagia or transient cervical weakness.[20-22]

Other less frequent uses included reduction of parotid gland volume through ultrasound-guided intraglandular injection, intraoperative platysma injection to improve cervical scar healing, and intranasal injection into the turbinates for intrinsic rhinitis, with favorable outcomes and few clinically relevant adverse events.[15,25,28] Finally, in cervical dystonia, ultrasound- or electromyography-guided injection into the deep cervical muscles showed comparable efficacy and an acceptable safety profile.[30]

Figure 2 summarizes the most widely used BoNT-A administration techniques according to the anatomical region treated. In the lower third of the face, multipoint intramuscular injection into the masseter predominated, whereas temporomandibular disorders were treated with combined injections into the masseter and temporalis muscles, occasionally under ultrasound guidance. In the cervical region, superficial injections targeting the platysmal bands and jawline were used most frequently, whereas ultrasound- or electromyography-guided techniques targeting the deep muscles were used for cervical dystonia. Finally, nasal and parotid applications involved localized injections intended to limit drug diffusion and the associated functional effects.[12-18,20-30]

Table 3. Technical characteristics and clinical outcomes of botulinum toxin type A administration according to anatomical region and therapeutic or aesthetic indication

Authors, year of publication	Anatomical region, indication	Type of BoNT-A	Dose used	Administration technique	Injection sites	Duration of effect	Main outcomes	Adverse events
Park et al.[12], 2022	Lower facial contouring	BoNT-A	25 U per masseter	Intramuscular injection + oral appliance	Bilateral masseter muscles in the lower third of the face	24 weeks	Significant reduction in facial volume and improvement in mandibular contour	Transient muscle fatigue
Lee et al.[13], 2015	Lower facial contouring, masseter hypertrophy	Botulax	25 U per masseter; second administration at 4 months	Bilateral intramuscular injection	Bilateral masseter muscles	> 6 months after the second administration	Greater reduction in facial volume and muscle thickness with 2 treatment sessions	Transient masticatory weakness
Lee et al.[14], 2024	Benign masseter hypertrophy	Botulax	24-96 U bilaterally	Bilateral intramuscular injection	3 injection sites per side	≈ 20 weeks	Reduction in masseter thickness and lower facial volume	No serious adverse events
Bae et al.[15], 2020	Post-thyroidectomy cervical scar healing	Nabota	50 U	Intraoperative injection	5 sites along the platysma muscle	24 weeks	Significant improvement in cervical scar appearance	No relevant adverse events
Liew et al.[16], 2024	Lower facial contouring	OnabotulinumtoxinA	24-96 U bilaterally	Deep intramuscular injection	3 injection sites per masseter	Up to 6 months	Reduction in facial width and increase in the mandibular angle	Mild masticatory dysfunction
Wei et al.[17], 2015	Masseter hypertrophy	BoNT-A	35 U per side	Bilateral intramuscular injection + masticatory exercises	Bilateral masseter muscles	Up to 12 months	Prolonged masseter-reducing effect	Local pain and mild weakness
Seok et al.[18], 2024	Masseter hypertrophy	PrabotulinumtoxinA	48 U total (24 U per side)	Intramuscular injection	Safe zone between the tragus and the oral commissure; 3 injection sites per side	Up to 24 weeks	Sustained reduction in muscle thickness and aesthetic improvement	Mild masticatory dysfunction
Fabi et al.[20], 2025	Platysmal prominence	OnabotulinumtoxinA	26-36 U	Superficial cervical injection	Platysmal bands and jawline	4-5 months	Significant improvement in cervical bands and mandibular definition	Erythema and cervical tenderness
Rohrich et al.[21], 2025	Cervical platysmal prominence	OnabotulinumtoxinA	26-72 U	Submandibular injection	Submandibular platysma and cervical bands	4-6 months	Significant aesthetic improvement of the neck	Transient mild dysphagia

(Continues)

Table 3. Technical characteristics and clinical outcomes of botulinum toxin type A administration according to anatomical region and therapeutic or aesthetic indication *(continued)*

Authors, year of publication	Anatomical region, indication	Type of BoNT-A	Dose used	Administration technique	Injection sites	Duration of effect	Main outcomes	Adverse events
Shridharani et al.[22], 2025	Platysmal bands, cervical rejuvenation	OnabotulinumtoxinA	26-36 U	Superficial injection	Cervical platysma and jawline	3-5 months	Significant improvement in cervical bands and mandibular definition	Mild dysphagia and local pain
De la Torre Canales et al.[23], 2022	TMD-related myofascial pain	BoNT-A	10–25 U into the temporalis + 30–75 U into the masseter	Bilateral intramuscular injection	Temporalis and masseter muscles	3-6 months	Improvement in pain and mandibular mobility	Local pain and masticatory weakness
De la Torre Canales et al.[24], 2024	Refractory myofascial pain	BoNT-A	80 U total	Bilateral intramuscular injection	5 injection sites per masseter and temporalis muscle	6 months	Significant pain reduction and psychosocial improvement	Mild muscle weakness
Kim et al.[25], 1998	Intrinsic rhinitis	Botox	4 U per nostril	Endoscopy-guided intranasal injection	Middle and inferior turbinates	≈ 4 weeks	Significant reduction in rhinorrhea	Mild nasal dryness
Carruthers et al.[26], 2025	Masseter hypertrophy	OnabotulinumtoxinA	24-96 U bilaterally	Deep intramuscular injection	3 injection sites per masseter	4-6 months	Reduction in masseter volume and facial slimming	Mild masticatory weakness and transient facial paresis
Ayala et al.[27], 2024	Muscular TMD	BoNT-A	80 U total	Bilateral intramuscular injection	3 injection sites in the masseter and 2 in the temporalis muscle on each side	6 months	Significant pain reduction without clinically relevant functional impairment	No serious adverse events
Jeong et al.[28], 2024	Parotid volume reduction, facial slimming	Botulax	15-30 U per parotid gland	US-guided injection	Bilateral superficial parotid glands	3 months	Significant reduction in parotid volume	No clinically significant xerostomia
Shabaan et al.[29], 2025	Masseter myofascial pain	OnabotulinumtoxinA	100 U total	Comparison of US-guided intraoral vs. extraoral injection	Trigger points in the masseter muscle	3-6 months	The intraoral technique provided greater pain relief and better quality of life	Transient local pain
Graciani et al.[30], 2025	Cervical dystonia	AbobotulinumtoxinA	417 ± 215 U	US- or EMG-guided administration	SCM, splenius, semispinalis, trapezius, levator scapulae, and deep cervical muscles	Variable according to clinical response	Similar improvement in TWSTRS scores with US and EMG guidance	No significant adverse events

BoNT-A: botulinum toxin type A; EMG: electromyography; SCM: sternocleidomastoid; TMD: temporomandibular disorders; TWSTRS: Toronto Western Spasmodic Torticollis Rating Scale; US: ultrasound.

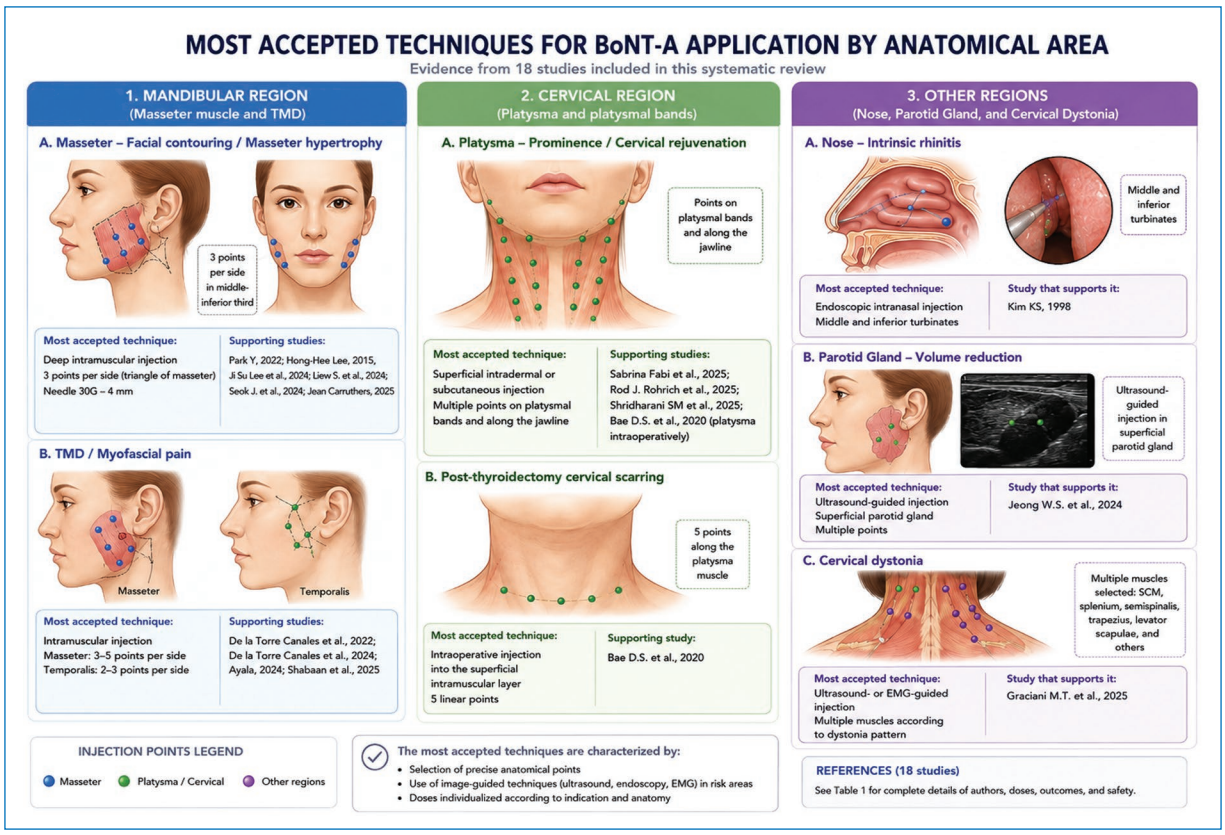

Figure 2. Most widely used botulinum toxin type A (BoNT-A) administration techniques according to the anatomical region treated.[13,20-26,29] SCM: sternocleidomastoid; EMG: electromyography; TMD: temporomandibular disorders.

Figure 3 summarizes a clinical algorithm intended to guide the use of BoNT-A in nonconventional anatomical regions of the middle and lower thirds of the face and the neck. It integrates the technical considerations derived from the evidence analyzed.

Safety profile and reported complications

Overall, the included studies reported a favorable safety profile for BoNT-A, with predominantly mild and transient adverse events. As shown in table 4, the most frequent complications were masticatory weakness, muscle fatigue, and local discomfort following injection into the masseter muscle, particularly in treatments for masseter hypertrophy and lower facial contouring.[12,13,16-18,26] In studies of temporomandibular disorders and myofascial pain, local edema, transient reduction in mandibular strength, smile asymmetry, and occasional episodes of mild dysphagia associated with diffusion into the perioral or cervical muscles were also reported.[23,27,29]

In cervical applications targeting the platysma, transient mild dysphagia and cervical weakness were the functional adverse effects of greatest clinical relevance, probably related to deep diffusion of the drug into the suprahyoid and cervical musculature.[21,22] Nevertheless, most studies reported no serious adverse events, particularly when superficial or ultrasound-guided techniques were used, as in cervical rejuvenation, parotid reduction, and cervical dystonia.[20,28,30] Other reported adverse effects included minimal xerostomia, mild nasal dryness, and transient facial paresis, without permanent functional consequences.[15,25]

Risk of bias

The risk-of-bias assessment using the RoB 2 tool (Table 5) showed that most of the included clinical trials raised "some concerns" in the overall assessment. The main limitations were identified in the randomization process and the selection of reported results, primarily because of insufficient information on allocation concealment, the absence of prospectively registered protocols, and a lack of clarity regarding statistical analysis plans. In addition, some studies raised concerns related

Table 4. General classification of adverse events according to frequency and severity

Authors, year of publication	Anatomical region, indication	Reported adverse events	Reported frequency	Severity	Possible mechanism	Functional impact
Park et al.[12], 2022	Lower facial contouring	Transient masticatory muscle fatigue	Low	Mild	Local diffusion into the deep masseter	Mild reduction in masticatory strength
Lee et al.[13], 2015	Masseter hypertrophy	Masticatory weakness, local discomfort	Frequent	Mild	Partial denervation of the masseter muscle	Fatigue during mastication
Lee et al.[14], 2024	Benign masseter hypertrophy	No serious adverse events reported	Very low	Mild	Limited diffusion with a controlled technique	No significant functional impairment
Bae et al.[15], 2020	Post-thyroidectomy cervical scar healing	No relevant adverse events	Very low	Mild	Localized injection into the superficial platysma	No functional impairment
Liew et al.[16], 2024	Lower facial contouring	Mild masticatory weakness, transient facial paresis	Low	Mild to moderate	Diffusion into the zygomaticus or risorius muscles	Temporary impairment of smiling and mastication
Wei et al.[17], 2015	Masseter hypertrophy	Local pain, masticatory weakness, mild facial asymmetry	Frequent	Mild	Unilateral diffusion or asymmetric masseter atrophy	Transient masticatory fatigue
Seok et al.[18], 2024	Masseter hypertrophy	Mild masticatory dysfunction	Low	Mild	Functional weakening of the masseter	Mild difficulty chewing hard foods
Fabi et al.[20], 2025	Platysmal prominence	Cervical erythema, local tenderness	Frequent	Mild	Local inflammatory reaction after injection	No relevant functional impairment
Rohrich et al.[21], 2025	Cervical platysmal prominence	Transient mild dysphagia, cervical weakness	Low to moderate	Moderate	Deep diffusion into the suprahyoid and cervical musculature	Transient difficulty swallowing
Shridharani et al.[22], 2025	Platysmal bands	Mild dysphagia, local pain	Low	Mild to moderate	Drug diffusion into the deep cervical muscles	Mild swallowing impairment
De la Torre Canales et al.[23], 2022	Myofascial pain, TMD	Local pain, masticatory weakness	Frequent	Mild	Excessive relaxation of the masseter and temporalis muscles	Reduced mandibular strength
De la Torre Canales et al.[24], 2024	Refractory myofascial pain	Local edema, muscle weakness, smile asymmetry, dysphagia	Moderate	Mild to moderate	Diffusion into the perioral and cervical muscles	Temporary impairment of smiling and swallowing
Kim et al.[25], 1998	Intrinsic rhinitis	Mild nasal dryness	Low	Mild	Local diffusion across the nasal mucosa	No significant functional impairment
Carruthers et al.[26], 2025	Masseter hypertrophy	Masticatory weakness, mild facial paresis	Moderate	Mild to moderate	Diffusion into the superficial facial muscles	Masticatory fatigue and mild impairment of facial expression
Ayala et al.[27], 2024	Muscular TMD	No serious adverse events reported	Very low	Mild	Localized intramuscular technique	No major functional impact

(Continues)

Table 4. General classification of adverse events according to frequency and severity *(continued)*

Authors, year of publication	Anatomical region, indication	Reported adverse events	Reported frequency	Severity	Possible mechanism	Functional impact
Jeong et al.[28], 2024	Parotid volume reduction	Minimal or no xerostomia	Very low	Mild	Diffusion limited to the glandular parenchyma	No significant impairment of salivary function
Shabaan et al.[29], 2025	Masseter myofascial pain	Transient local pain	Frequent	Mild	Mechanical needle trauma and limited local diffusion	No persistent functional impairment
Graciani et al.[30], 2025	Cervical dystonia	No significant adverse events reported	Very low	Mild	US- or EMG-guided administration reduced inadvertent diffusion	No relevant functional deterioration

EMG: electromyography; TMD: temporomandibular disorders; US: ultrasound.

to deviations from the intended interventions, particularly in unblinded studies or those providing limited information on adherence and cointerventions. By contrast, the domains of missing outcome data and outcome measurement were predominantly rated as having a low risk of bias, suggesting adequate collection and assessment of clinical outcomes. Two studies were classified as having a high overall risk of bias because of major methodological limitations during the intervention, whereas only 1 trial was rated as having a low risk across all assessed domains. Overall, the available evidence has moderate methodological limitations that should be considered when interpreting findings on the efficacy and safety of BoNT-A in nonconventional regions of the middle and lower thirds of the face and the neck.

Discussion

The present systematic review demonstrates that BoNT-A is an effective and safe alternative for various nonconventional applications involving the middle and lower thirds of the face and the neck. The evidence was particularly consistent for masseter hypertrophy, for which several randomized clinical trials showed significant reductions in muscle thickness, facial volume, and mandibular prominence, with benefits sustained for several months.[12-14,16-18,26] Similarly, studies evaluating platysmal prominence demonstrated clinically relevant aesthetic improvements compared with placebo, consolidating BoNT-A as a minimally invasive option for cervical rejuvenation.[20-22]

Furthermore, the findings observed in temporomandibular disorders suggest a favorable therapeutic effect. The included studies reported significant reductions in pain, improved mandibular mobility, and better quality of life in patients with persistent or refractory myofascial pain.[23,24,27,29] Nevertheless, the magnitude of benefit varied among studies, probably because of differences in the doses used, the muscles treated, and the diagnostic criteria applied. This heterogeneity makes it difficult to establish uniform recommendations for clinical practice.

Moreover, emerging evidence was identified for other less extensively studied applications. Intranasal BoNT-A injection showed benefits in controlling rhinorrhea in patients with intrinsic rhinitis,[25] whereas injection into the parotid gland reduced glandular volume without causing clinically relevant xerostomia.[28] Similarly, intraoperative injection into the platysma improved the quality of cervical scar healing after thyroidectomy,[15] thereby expanding the therapeutic potential of BoNT-A beyond its traditional aesthetic indications.

Although all BoNT-A formulations demonstrated clinical efficacy, some relevant differences were observed. OnabotulinumtoxinA was the most extensively studied formulation and showed consistent evidence for both masseter hypertrophy and platysmal prominence, with effects lasting between 4 and 6 months and improvements exceeding 75% for some aesthetic outcomes. PrabotulinumtoxinA had a mean duration of effect of approximately 20 weeks and produced a reduction in lower facial volume of up to 9.2%, whereas letibotulinumtoxinA showed favorable results mainly in reducing masseter thickness, with a more evident response at doses ≥ 48 U. These differences suggest possible variations in the duration of effect and the required dosing regimens. However, the absence of direct comparative studies precludes determining whether any formulation offers clinically significant advantages over the others.[14,16,20-22,26,30]

Table 5. Risk of bias of the included studies (RoB 2)

Authors, year of publication	Domain 1	Domain 2a	Domain 2b	Domain 3	Domain 4	Domain 5	Overall risk of bias
Park et al.[12], 2022	Low risk of bias	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Some concerns	Some concerns
Lee et al.[13], 2015	Some concerns	Some concerns	Some concerns	Low risk of bias	Low risk of bias	Some concerns	Some concerns
Lee et al.[14], 2024	Some concerns	Some concerns	Some concerns	Low risk of bias	Some concerns	Some concerns	Some concerns
Bae et al.[15], 2020	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Some concerns
Liew et al.[16], 2024	Some concerns	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Some concerns	Some concerns
Wei et al.[17], 2015	Some concerns	High risk of bias	Some concerns	Low risk of bias	Some concerns	Some concerns	High risk of bias
Seok et al.[18], 2024	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Some concerns
Fabi et al.[20], 2025	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Rohrich et al.[21], 2025	Low risk of bias	Some concerns	Low risk of bias	Some concerns	Low risk of bias	Some concerns	Some concerns
Shridharani et al.[22], 2025	Low risk of bias	Some concerns	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Some concerns
De la Torre Canales et al.[23], 2022	Low risk of bias	Some concerns	Some concerns	Some concerns	Low risk of bias	Some concerns	Some concerns
De la Torre Canales et al.[24], 2024	Low risk of bias	Some concerns	Some concerns	Some concerns	Low risk of bias	Some concerns	Some concerns
Kim et al.[25], 1998	Low risk of bias	Some concerns	Some concerns	Some concerns	Low risk of bias	Some concerns	Some concerns
Carruthers et al.[26], 2025	Some concerns	Some concerns	Low risk of bias	Some concerns	Low risk of bias	Some concerns	Some concerns
Ayala et al.[27], 2024	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	Some concerns
Jeong et al.[28], 2024	Some concerns	Some concerns	Some concerns	Some concerns	Low risk of bias	Some concerns	Some concerns
Shabaan et al.[29], 2025	Some concerns	Low risk of bias	Some concerns	High risk of bias	Low risk of bias	Some concerns	High risk of bias
Graciani et al.[30], 2025	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Some concerns	High risk of bias

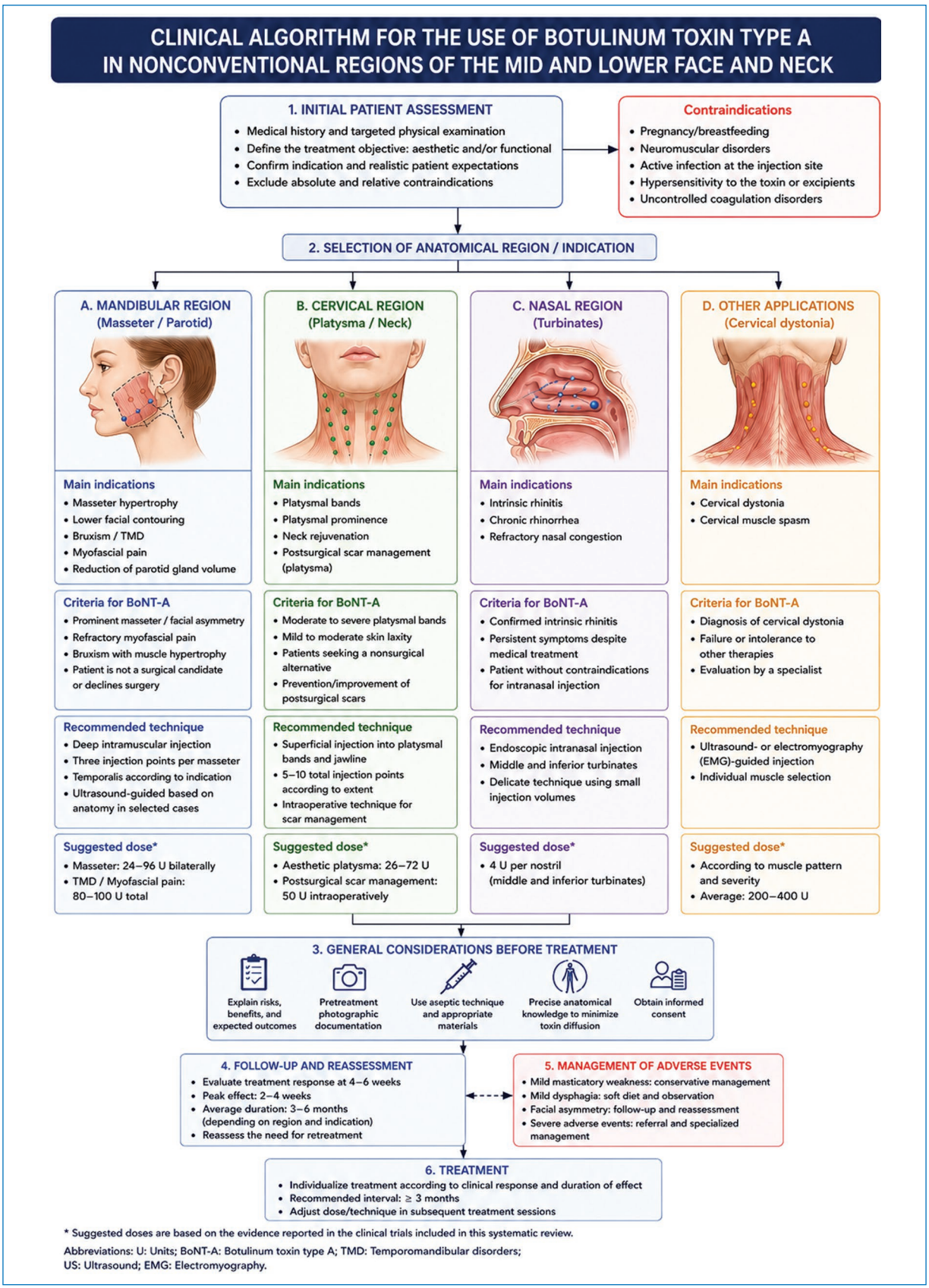

Figure 3. Clinical algorithm for the use of botulinum toxin type A (BoNT-A) in nonconventional anatomical regions of the middle and lower thirds of the face and the neck. TMD: temporomandibular disorders; US: ultrasound.

A strength of this review is the exclusive inclusion of randomized clinical trials, which provides evidence of higher methodological quality. However, the heterogeneity in the formulations used, administered doses, injection techniques, and assessed outcomes limits direct comparisons among studies. In addition, most trials reported follow-up periods < 6 months, restricting the evaluation of long-term safety and efficacy profile.

From a clinical perspective, the findings support the use of BoNT-A for selected indications involving the lower thirds of the face and the neck when patients are appropriately selected and the clinician has precise knowledge of regional anatomy. Future studies should focus on standardizing administration protocols, defining optimal doses, and evaluating long-term outcomes to strengthen the available evidence.

Study limitations

The present systematic review identified substantial heterogeneity among the included studies in terms of indications, doses, administration techniques, treated anatomical regions, and assessment methods, which hinders direct comparison of the results and the identification of standardized protocols. Likewise, variability in clinical outcomes and follow-up periods precluded conducting a meta-analysis. Most studies had moderate sample sizes and limited follow-up periods, restricting the assessment of long-term efficacy and safety. Finally, publication bias cannot be ruled out and may have influenced the magnitude of the observed benefits.

Conclusions

The available evidence indicates that BoNT-A is a safe and effective intervention for various nonconventional applications involving the middle and lower thirds of the face and the neck, with particularly consistent results for masseter hypertrophy, platysmal prominence, and certain temporomandibular disorders.

From a clinical perspective, these findings support its use as a minimally invasive therapeutic alternative for facial and cervical contouring, as well as for the management of selected patients with refractory myofascial pain.

Variability in doses, administration techniques, and assessed outcomes limits the standardization of clinical recommendations. Therefore, multicenter clinical trials with prolonged follow-up and uniform protocols are needed to define optimal therapeutic regimens, establish recommendations based on high-quality evidence, and promote more consistent implementation of these applications in clinical practice.

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The authors declare that this study was conducted using their own resources.

Conflicts of interest

The authors declared no conflicts of interest whatsoever.

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. This study did not involve personal data, medical records, or human biological samples and therefore did not require ethical approval. The SAGER guidelines were not applicable.

Declaration on the use of artificial intelligence. The authors declare that a generative artificial intelligence tool (ChatGPT, OpenAI) was used to assist with content organization and the initial drafting of certain sections of the manuscript – namely, the introduction, systematic-review methodology, discussion, and preparation of summaries – as well as to improve the language and clarity of the text. The tool was used solely for editorial support and was not used for the literature search, article selection, data analysis, or interpretation of the results. All content generated or assisted by artificial intelligence was critically reviewed, verified, and edited by the authors, who assume full responsibility for the scientific content, interpretation of the data, and conclusions of the manuscript.

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REVIEW ARTICLE

Methotrexate in pediatric dermatology: an old acquaintance, new certainties

Metotrexato en dermatología pediátrica: viejo conocido, nuevas certezas

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Abstract

Methotrexate (MTX) is a folic acid antagonist with antiproliferative, antiinflammatory, and immunosuppressive effects, widely used in pediatric dermatology for the management of inflammatory and immune-mediated diseases. The objective of this review is to establish, based on current evidence, the status and utility of methotrexate in pediatric dermatology. A narrative literature review was conducted using electronic databases PubMed, Scopus, and SciELO, covering articles published in English and Spanish between 2000 and 2025. The search included the keyword "methotrexate" combined with "pediatric dermatology," "psoriasis," "atopic dermatitis," "morphea," and "alopecia areata," as well as terms related to its "history" and "pharmacokinetics." Clinical studies, systematic reviews, clinical practice guidelines, and relevant case series were included. Duplicate articles, studies conducted exclusively in adult populations, and those without full-text access were excluded. At low doses, MTX has demonstrated efficacy and safety in conditions such as psoriasis, severe atopic dermatitis, morphea, and alopecia areata, positioning it as a first-line therapeutic option. It is primarily administered orally at doses ranging from 0.2 to 1 mg/kg/week and requires regular monitoring with complete blood count and liver and renal function tests to prevent complications. Folic acid supplementation has been shown to reduce the frequency and severity of adverse effects, particularly gastrointestinal and hematologic events. Although the use of biologic therapies has increased over the past decade, MTX remains an accessible, cost-effective treatment with strong clinical support in the pediatric population.

Keywords: *Methotrexate. Child. Atopic dermatitis. Localized scleroderma. Alopecia areata. Dermatology.*

Resumen

El metotrexato (MTX) es un antagonista del ácido fólico con efectos antiproliferativos, antiinflamatorios e inmunosupresores, ampliamente utilizado en dermatología pediátrica para el manejo de enfermedades inflamatorias e inmunomediadas. El objetivo de esta revisión es establecer, conforme a la evidencia actual, el estatus y la utilidad del metotrexato en dermatología pediátrica. Se realizó una revisión narrativa de la literatura mediante búsqueda en las bases de datos electrónicas PubMed, Scopus y SciELO, incluyendo artículos publicados en inglés y español entre 2000 y 2025. Se empleó como término clave "methotrexate" combinado con "pediatric dermatology", "psoriasis" "atopic dermatitis", "morphea" y "alopecia areata", así como términos relacionados con "historia" y "farmacocinética". Se incluyeron estudios clínicos, revisiones sistemáticas, guías de práctica clínica y series de casos relevantes. Se excluyeron artículos duplicados, estudios en población exclusivamente adulta y aquellos sin acceso a texto completo. En dosis bajas, el MTX ha demostrado eficacia y seguridad en patologías como la psoriasis, la dermatitis atópica grave, la morfea y la alopecia areata, posicionándose como una opción terapéutica

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de primera línea. Su administración es principalmente por vía oral, con un rango de dosificación de 0.2-1 mg/kg/semana, y requiere monitorización periódica mediante biometría hemática y pruebas de función hepática y renal para prevenir complicaciones. La suplementación con ácido fólico ha demostrado disminuir la frecuencia y la gravedad de los efectos adversos, principalmente gastrointestinales y hematológicos. Aunque el uso de terapias biológicas se ha incrementado en la última década, el MTX continúa siendo una alternativa accesible, costo-efectiva y con amplio respaldo clínico en población pediátrica.

Palabras clave: *Metotrexato. Niño. Dermatitis atópica. Esclerodermia localizada. Alopecia areata. Dermatología.*

Introduction

Methotrexate (MTX) is a drug with a long history in medicine and is used for both its antineoplastic properties and its immunomodulatory effects. Several medical specialties, including oncology, immunology, rheumatology, and dermatology, use it to treat multiple diseases. It is a folic acid antagonist that has proven particularly useful in dermatology for controlling immune-mediated diseases.[1]

In pediatric dermatology, MTX has progressively become part of the therapeutic armamentarium, supported by a growing body of evidence demonstrating its safety and efficacy. However, questions remain regarding the optimal regimens for its initiation, maintenance, and discontinuation, highlighting the need to understand the currently available information on this drug.[2]

The objective of this review is to examine the current role of MTX in pediatric dermatology, its most common indications, and current recommendations for its use. Although alternatives such as biologic therapies have emerged in recent years, MTX remains widely used because of its accessibility, low cost, and well-established long-term safety profile.[1,2]

History

MTX was initially approved by the US Food and Drug Administration in 1953 for the treatment of acute lymphoblastic leukemia in adults. It subsequently became established as an antineoplastic drug used to treat various types of cancer, including lymphomas, osteosarcoma, and carcinomas, in both adult and pediatric patients.[3]

Its use in dermatology began around the 1970s, primarily for the treatment of psoriasis in adults, following studies demonstrating its immunosuppressive and antiproliferative effects.[4] In pediatrics, MTX use outside the oncology setting began with the treatment of juvenile idiopathic arthritis, in which it proved effective as a disease-modifying drug.[5] Its use was subsequently extended to multiple pediatric dermatologic diseases, most commonly moderate-to-severe psoriasis, refractory atopic dermatitis, morphea, and severe alopecia areata.[2]

Because of the broad range of indications and its use across different specialties, there is considerable variability in initiation, maintenance, discontinuation, and monitoring regimens. A recent evidence-based consensus developed by the Pediatric Dermatology Research Alliance proposed standardized recommendations for its use in pediatric patients, including criteria for patient selection, dosing, follow-up, and monitoring.[2]

Notably, although many uses of MTX in pediatric dermatology have not received specific approval from the US Food and Drug Administration or other regulatory agencies, numerous scientific studies and case series support its safety and efficacy. This evidence has established MTX as a fundamental therapeutic option for pediatric immune-mediated diseases.

Pharmacology

Mechanism of action

MTX has 3 mechanisms of action:

- Antiproliferative: it inhibits dihydrofolate reductase, thereby blocking the synthesis of deoxythymidylic acid and, consequently, DNA and RNA replication. This is the predominant effect at high doses.
- Anti-inflammatory: at low doses, it inhibits 5-aminoimidazole-4-carboxamide ribonucleotide transformylase, resulting in the accumulation of adenosine, which modulates inflammation.[6]
- Immunosuppressive: it inhibits the Janus kinase/signal transducer and activator of transcription pathway, thereby reducing the transcription of proinflammatory cytokines. It also reduces tumor necrosis factor α, interleukin 1β, interleukin 6, and adhesion molecules such as E-selectin and vascular cell adhesion molecule 1, while increasing interleukin 10-producing T lymphocytes and modulating the immune response.[7,8]

Pharmacokinetics

– Absorption: after oral administration, MTX is absorbed through the proximal jejunum via the proton-coupled folate transporter/SLC46A1, with a bioavailability of 64%-90% and a plateau effect. Subcutaneous administration provides better absorption and avoids this plateau effect. Pharmacokinetic profiles differ between oral and subcutaneous MTX only during the first 2-3 months of treatment, after which they are generally similar.[9]
– Distribution: approximately 50% is bound to plasma proteins. MTX crosses the placenta and accumulates in the liver and kidneys.
– Metabolism: during first-pass hepatic metabolism, MTX is converted to 7-hydroxymethotrexate, its main metabolite, which is subsequently excreted by the kidneys.
– Excretion: MTX is eliminated primarily by the kidneys. Renal impairment, ascites, and pleural effusions reduce its elimination and increase the risk of toxicity.
– Half-life: despite its short plasma half-life of 6-8 hours, intracellular MTX polyglutamates have been identified in erythrocytes, neutrophils, and monocytes. These are considered the active form of MTX and may remain detectable for up to 1 week after administration.[10]

Dosing in pediatric dermatology

MTX use can be classified into 2 categories according to dose – high-dose and low-dose regimens – which have different effects and applications:

– High-dose regimens: these average 1 g/m^2 or exceed 5 mg/kg and are used primarily to treat malignant neoplasms. They have marked antineoplastic effects and are associated with risks such as bone marrow aplasia, hepatotoxicity, alopecia, and infection. These doses are not used in pediatric dermatology.
– Low-dose regimens: these are used for inflammatory and immune-mediated diseases and generally range from 7.5-30 mg/wk, equivalent to 10-20 mg/m^2/wk or ≤ 1 mg/kg/wk. These are the doses used primarily in pediatric dermatology. Although there is no consensus regarding the exact starting dose, pediatric studies and guidelines report ranges of 0.3-0.5 mg/kg/wk, with a maximum dose of 1 mg/kg/wk, up to 25-30 mg/wk.[6,11,12]

These dosing regimens are based on those used for juvenile idiopathic arthritis because of the accumulated experience in pediatric patients. Adult doses range from 10-25 mg/wk. Within this range, lower doses are better tolerated but produce a slower response, whereas higher doses act more rapidly but are less well tolerated.[5]

Table 1. Methotrexate dosing recommendations in pediatric dermatology

Dosing method	Starting dose	Maintenance dose
mg/kg/wk	0.2-0.4	0.4-1
mg/m^2/wk	5-10	10-20

In pediatric patients, MTX may be dosed according to body weight or body surface area. Several studies have investigated which method is preferable, but no clear preference has been established. Current consensus recommendations favor dosing in mg/kg/wk for diseases such as atopic dermatitis and in mg/m^2/wk for diseases such as psoriasis, although this distinction may reflect substantial heterogeneity among studies and the lack of direct comparisons between the 2 methods.[9,13] In most cases, weight-based dosing in mg/kg/wk is preferred because it simplifies calculations and reduces calculation errors, although body surface area-based dosing may be more precise.[13]

Treatment initiation at 2.5 mg/wk is recommended, followed by weekly increases of 2.5 mg until the target dose is reached, to reduce drug-related adverse effects.[2,14] Test doses should not be used for > 1 week because they have not been shown to predict subsequent adverse events.[1,2] The prescribed dose is often rounded to the nearest multiple of 2.5 mg to match the available formulations. The dose is administered as a single weekly dose, although some protocols divide the total dose into 2 consecutive administrations during the week to improve tolerability and bioavailability.[14] (Table 1).

Available routes of administration include oral, subcutaneous, intramuscular, and intravenous administration. The oral route is preferred because of its convenience and acceptability in children. When there is no response to oral administration, switching to the subcutaneous route may be considered before discontinuing MTX. Subcutaneous administration generally provides better tolerability than oral administration, and weekly doses also range from 15-25 mg.[9] No association has been found between administration with food and MTX efficacy.[13,15,16]

Baseline studies and monitoring

Before initiating MTX in pediatric patients with inflammatory skin diseases, a baseline assessment is

recommended, including a complete blood count, aspartate aminotransferase, alanine aminotransferase, and creatinine levels, as well as pregnancy testing in adolescents and women of childbearing potential. Tuberculosis testing and serologic testing for hepatitis B and C are not routinely required unless specific risk factors are present.[1,2]

After treatment initiation, follow-up laboratory testing using the same assessments is recommended after 1 month and subsequently every 3-4 months. The objective is to monitor efficacy, identify early adverse effects, and optimize treatment safety and benefit.[2]

Plasma MTX measurement may be used to assess short-term adherence but is neither routinely used nor recommended in clinical practice for low-dose regimens because of the drug's short half-life, pharmacokinetic variability, and the risk of incorrectly interpreting adherence. Quantification of 7-hydroxymethotrexate provides information on drug intake and metabolism, whereas intracellular MTX polyglutamates reflect long-term adherence. However, these analyses are complex and costly.[17]

Adverse effects and contraindications

MTX may cause adverse effects that vary according to the administered dose. High doses, which are not used in pediatric dermatology, are associated with hepatotoxicity, including cirrhosis and liver failure; pulmonary toxicity; gastrointestinal toxicity, including hemorrhagic enteritis and intestinal perforation; and an increased risk of lymphoma and infections. Low doses may cause gastrointestinal symptoms, including nausea, anorexia, diarrhea, and dyspepsia; mucositis; stomatitis; fatigue; and headache. Other very rare adverse effects include hypersensitivity reactions, impaired drug elimination, hepatic fibrosis, and pulmonary fibrosis.[18]

Transient elevations in aminotransferase levels may occur during the first few days after MTX administration. Therefore, laboratory testing should be avoided during the first 3 days after a dose. Temporary discontinuation of MTX is indicated when aminotransferase levels exceed 3 times the upper limit of normal for 2 consecutive months. Concomitant use of hepatotoxic drugs at high doses, such as acetaminophen, should also be avoided. Cytopenias and bone marrow aplasia are uncommon with low-dose MTX.[19]

Absolute contraindications include pregnancy, breastfeeding, and liver failure. Relative contraindications include alcohol consumption, renal impairment, and mild liver disease. In the presence of moderate or severe infections, treatment should be temporarily discontinued until the patient has recovered. Recent studies have reported that approximately 46.7% of patients experience persistent adverse effects, with gastrointestinal effects being the most frequent.[1]

Folic acid supplementation is an effective strategy for reducing the prevalence and severity of these adverse effects and improving treatment tolerability. Folinic acid is converted directly into tetrahydrofolate and therefore acts more rapidly when symptoms are already present.

In pediatric patients with psoriasis, daily folic acid administration has been shown to reduce MTX-related adverse events compared with weekly administration.[20] Folic acid at a dose of 1 mg/d is recommended regardless of body weight and age. If symptoms persist, the dose may be increased to 5 mg/d.[2] Clinical trials have shown that folic acid supplementation 6 or 7 times per week reduces the prevalence of persistent adverse effects, particularly gastrointestinal effects, compared with weekly administration.[21,22]

Drug interactions

Despite the many isolated cases reported in the literature, few drugs are truly contraindicated for concomitant use with low-dose MTX.[2] (Table 2). One such drug is trimethoprim-sulfamethoxazole because of the theoretical risk of potentiating inhibition of the folic acid pathway. However, few cases involving low-dose MTX support this contraindication.[2,11]

Enhancement of effect

Combining certain drugs with MTX may allow the MTX dose to be reduced and, consequently, lower the risk of adverse effects while improving therapeutic efficacy. Consensus recommendations support combining MTX with agents such as azathioprine, mycophenolate, and corticosteroids.[2] The combined or sequential use of MTX and biologic agents remains an area of active investigation. Direct comparisons between MTX and biologic agents in pediatric psoriasis have shown that biologic agents are more effective and are associated with lower treatment discontinuation rates.

A comparative study of children with psoriasis treated with MTX or biologic agents, such as adalimumab and etanercept, found a greater reduction in psoriasis severity with biologic therapy. In addition to their documented efficacy, biologic agents require less monitoring and are

Table 2. Main drug interactions with methotrexate in pediatric dermatology

Type of interaction	Drug or substance	Recommendation	Level of evidence*
Vaccines	MMR vaccine	Not contraindicated	BII
	VZV vaccine	Not contraindicated	BII
Antibiotics	Trimethoprim-sulfamethoxazole	Not contraindicated, although additional monitoring should be considered in specific cases	CIII
	Penicillins, tetracyclines, chloramphenicol, clindamycin	May be administered without additional monitoring for drug interactions	CIII
Anti-inflammatory and immunomodulatory agents	NSAIDs and salicylates	May be used if renal function is normal	BII
	Acitretin	Concomitant use is permitted	CIII
	Systemic corticosteroids	No clinically relevant pharmacokinetic interactions	BII
	Azathioprine, mycophenolate mofetil	No clinically relevant pharmacokinetic interactions	BII
	Cyclosporine	Use with caution	No consensus
Other agents	Probenecid, phenytoin	Limited evidence, with a theoretical risk or isolated reports of toxicity	No consensus
	Hepatotoxic herbal products	Avoid because of the risk of hepatotoxicity	CIII
	Alcohol	Avoid because of the risk of hepatotoxicity	CIII

*The level of evidence is based on the US Public Health Service grading system. The letter indicates the strength of the recommendation (A, strong; B, moderate; C, weak), and the Roman numeral indicates the quality of evidence (I, randomized clinical trials; II, well-designed nonrandomized studies or cohort studies; III, expert opinion or case series).
MMR: measles, mumps, and rubella; NSAIDs: nonsteroidal anti-inflammatory drugs; VZV: varicella-zoster virus.

associated with fewer MTX-related toxic effects. However, biologic drugs are substantially more expensive and less accessible than MTX.[23]

Although biologic agents are generally more effective than MTX, a substantial proportion of patients respond favorably to MTX. Therefore, identifying potential non-responders or combining MTX with biologic agents may improve the cost-effectiveness of therapy. A subsequent analysis of the comparative trial of adalimumab and MTX evaluated withdrawal and retreatment periods. Patients treated sequentially with MTX and adalimumab achieved better clinical scores than those treated with biologic therapy alone.[24] However, not all studies have shown that concomitant treatment with biologic agents and MTX is more effective than biologic monotherapy.[1,24]

Response to treatment

It is important to recognize that the response to MTX is not immediate. In most diseases, a clinical response is expected within 2-3 months. Therefore, concomitant drugs, such as corticosteroids, are recommended during the first weeks of treatment to stabilize the disease.[13,15,18]

Methotrexate discontinuation

Some authors do not recommend abrupt discontinuation of MTX because of the risk of disease relapse, although no other risks have been associated with sudden withdrawal.[14] Once the therapeutic goal has been achieved, the duration of MTX treatment depends on the specific disease and the time required to maintain disease control. When MTX dose reduction is planned, weekly tapering regimens are generally recommended, although some authors consider that treatment may be discontinued abruptly without major consequences.[13,14] There is no established maximum duration of MTX use as long as treatment remains effective and well tolerated.

Immunizations

Routine vaccination schedules are recommended for patients receiving doses < 0.4 mg/kg/wk. At higher doses, live attenuated vaccines, including measles, rubella, mumps, varicella-zoster, and rotavirus vaccines, among others, are not recommended. For influenza, this recommendation applies only to the live attenuated

intranasal vaccine, whereas the inactivated intramuscular vaccine may be administered safely.[2,25]

Uses in pediatric dermatology

From a regulatory standpoint, MTX is not specifically approved by the US Food and Drug Administration or the European Medicines Agency for any pediatric dermatologic disease. Its use in pediatric dermatology is off-label and is based primarily on clinical evidence and medical practice guidelines. The most common indications in pediatric dermatology are atopic dermatitis, psoriasis, morphea, and alopecia areata. Other diseases for which evidence is more limited, but for which MTX may be useful as second-line or adjunctive therapy, include dermatomyositis, lichen planus, eosinophilic fasciitis, pityriasis rubra pilaris, pityriasis lichenoides chronica, bullous pemphigoid, lymphomatoid papulosis, cutaneous polyarteritis nodosa, cutaneous T-cell lymphoma, sarcoidosis, granuloma annulare, graft-versus-host disease, lichen sclerosus, chronic urticaria, vitiligo, systemic sclerosis, and systemic lupus erythematosus.[1,2,26] (Table 3).

Atopic dermatitis

Atopic dermatitis is a chronic inflammatory skin disease affecting 5%-20% of the pediatric population and 2%-5% of adults. Most patients have mild-to-moderate disease that can usually be controlled with topical therapies or phototherapy. However, a small subgroup does not respond to first-line treatments and requires systemic therapy. In this setting, MTX is used as a systemic alternative, particularly in patients with moderate-to-severe atopic dermatitis.[27,28]

Although few randomized controlled trials are available and the evidence is based mainly on retrospective studies, the findings indicate that MTX is effective and safe in pediatric patients. Documented clinical response rates range from 53.8% to 93%, with improvement > 75% in most cases, generally observed after 4-12 weeks of treatment.

A retrospective study of 55 pediatric patients treated with low-dose MTX at 0.4 mg/kg/wk reported clinical improvement in 76.4%.[29] Atopic dermatitis has been found to require higher MTX doses than other inflammatory diseases, such as psoriasis.[13,30] Recommended maintenance doses for pediatric atopic dermatitis are 0.7-1 mg/kg/wk, without exceeding 25 mg/wk.[13]

Psoriasis

Psoriasis is a chronic inflammatory skin disease and remains one of the main indications for MTX in dermatology in both adults and children. The US Food and Drug Administration has approved MTX for severe, recalcitrant, or treatment-resistant psoriasis in adults and for associated psoriatic arthritis in adults. In children, MTX is considered the first-line systemic drug when topical or other systemic treatments have failed to achieve adequate disease control or when joint involvement is present.[31] Several studies have shown favorable clinical outcomes in children with psoriasis. Approximately 50% of patients achieved at least a 75% reduction in the Psoriasis Area and Severity Index, corresponding to PASI 75, after 24 weeks of treatment. Treatment discontinuation after 48 weeks was mainly due to complete clearance and, less frequently, to adverse effects or lack of efficacy.[32]

A consensus statement recommends initiating MTX for pediatric psoriasis at 10 mg/m^2/wk, with a maximum dose of 15 mg/m^2/wk. If treatment is ineffective, switching from oral to subcutaneous administration is recommended.[31]

MTX remains a cornerstone of systemic treatment for pediatric psoriasis because of its efficacy, established safety profile, and extensive clinical experience, as supported by international guidelines and recent reviews.[1,6,33]

Morphea

Morphea, or localized scleroderma, is an inflammatory connective tissue disease characterized by skin thickening. Its recurrent course and possible extracutaneous involvement may lead to functional deformity and impaired quality of life.[34]

Consensus protocols for pediatric patients with linear morphea recommend MTX at 1 mg/kg/wk, with a maximum dose of 25 mg/wk, to optimize efficacy while minimizing adverse effects.[35] The available evidence supports its effectiveness. A randomized clinical trial showed that the combination of MTX and oral prednisone produced a significantly greater response than prednisone alone. Case series have reported disease inactivity with MTX response in 50 of 65 patients.[36,37]

Overall, these findings support MTX as a first-line systemic therapy for active pediatric morphea, particularly linear or extensive forms, with a favorable safety and efficacy profile when appropriate monitoring is performed.

Table 3. Indications for methotrexate use in pediatric dermatology

Category	Condition	Comments	Level of evidence*
Most common indications	Atopic dermatitis	Systemic treatment option for severe or refractory disease	BII
	Psoriasis	Systemic treatment option for moderate-to-severe disease, particularly extensive plaque psoriasis or associated psoriatic arthritis	BII
	Morphea (localized scleroderma)	Useful in linear or generalized forms; frequently combined with systemic corticosteroids	BII
	Alopecia areata	Growing evidence in extensive disease, including alopecia totalis and universalis. May be combined with other immunomodulatory treatments	BII
Second-line or adjunctive therapy	Juvenile dermatomyositis	Adjunctive treatment for cutaneous and systemic disease	CII
	Lichen planus	Used in extensive or treatment-resistant disease	CIII
	Eosinophilic fasciitis	Used in cases refractory to systemic corticosteroids	CIII
	Pityriasis rubra pilaris	Reported to be effective in some pediatric cases	CIII
	Pityriasis lichenoides chronica	Treatment option for persistent or recurrent disease	CIII
	Bullous pemphigoid	Adjunctive treatment for extensive disease	CIII
	Cutaneous polyarteritis nodosa	Second-line treatment for resistant disease	CIII
	Cutaneous T-cell lymphoma	Systemic immunomodulatory treatment in selected cases	CIII
	Cutaneous sarcoidosis	Limited but favorable evidence in treatment-resistant cases	CIII
	Granuloma annulare	Therapeutic alternative for generalized disease	CIII
	Graft-versus-host disease	Adjunctive immunosuppressive treatment	CIII
	Lichen sclerosus	Used in cases refractory to topical therapy	CIII
	Vitiligo	Adjunctive treatment for extensive or refractory disease	CIII
	Systemic sclerosis	Immunomodulatory treatment in juvenile forms	CIII
	Systemic lupus erythematosus	Adjunctive treatment for refractory cutaneous manifestations	CIII

*The level of evidence is based on the US Public Health Service grading system. The letter indicates the strength of the recommendation (A, strong; B, moderate; C, weak), and the Roman numeral indicates the quality of evidence (I, randomized clinical trials; II, well-designed nonrandomized studies or cohort studies; III, expert opinion or case series).

Alopecia areata

Alopecia areata is an autoimmune disorder characterized by hair loss that affects both pediatric and adult populations. MTX has been investigated as a treatment option in children with this condition, although available studies have included small samples.[38] A meta-analysis evaluated 16 studies that included pediatric and adult patients with alopecia areata treated with MTX.[39] The findings showed greater efficacy in adults, with good-to-complete hair regrowth, defined as 50%-100%, in 69.3% of adults and 46.5% of pediatric patients.[39] These data suggest that MTX may be effective in children, although the response is generally lower than in adults. Further research involving larger pediatric cohorts is needed to establish optimal treatment protocols.[40,41]

Conclusions

MTX remains a fundamental therapeutic option in pediatric dermatology, supported by decades of clinical experience and a growing body of evidence confirming its efficacy and safety at low doses. Despite the emergence of biologic agents and small molecules, which may provide faster responses and selective safety advantages in specific settings, MTX remains a first-line option for most pediatric patients, particularly when accessibility, cost-effectiveness, and long-term

experience are prioritized. Its rational, protocol-based, and evidence-based use is therefore essential, not only as initial therapy but also as maintenance treatment for numerous immune-mediated dermatologic diseases.

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Conflicts of interest

The authors declared no conflicts of interest whatsoever.

Ethical considerations

Protection of human participants and animals. The authors declare that no experiments involving humans or animals were conducted for this study.

Confidentiality, informed consent, and ethical approval. This study did not involve patients' personal data and did not require ethics approval. The SAGER guidelines were not applicable.

Declaration regarding the use of artificial intelligence. The authors declare that no generative artificial intelligence tools were used in the preparation of this manuscript.

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CLINICAL CASE

Chronic paracoccidioidomycosis: series of five clinical cases

Paracoccidioidomicosis crónica: serie de cinco casos clínicos

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Abstract

Paracoccidioidomycosis is a systemic disease caused by the fungus Paracoccidioides brasiliensis complex and Paracoccidioides lutzii, endemic in Latin America. Depending on the patient's immunological status, it can present as a chronic adult form or an acute juvenile form. Five clinical cases of chronic paracoccidioidomycosis treated in a public hospital in Argentina between November 2019 and October 2022 are described. Due to its wide variety of nonspecific mucocutaneous manifestations, clinical suspicion is essential for early diagnosis, initiation of antifungal treatment, and reduction of disabling sequelae and mortality.

Keywords: *Paracoccidioidomycosis. Paracoccidioides sp. Endemic mycosis. Neglected disease.*

Resumen

La paracoccidioidomicosis es una enfermedad sistémica causada por el hongo del complejo Paracoccidioides brasiliensis y Paracoccidioides lutzii, endémica en América Latina. Según el estado inmunitario del paciente puede presentarse como una forma crónica del adulto o aguda juvenil. Se describen cinco casos clínicos de paracoccidioidomicosis crónica atendidos en un hospital público de Argentina, entre noviembre del 2019 y octubre del 2022. Por su amplia variedad de manifestaciones mucocutáneas inespecíficas, es imprescindible la sospecha clínica para llegar al diagnóstico de manera precoz, iniciar el tratamiento antifúngico y así disminuir las secuelas incapacitantes y la mortalidad.

Palabras clave: *Paracoccidioidomicosis, Paracoccidioides sp. Micosis endémica. Enfermedad desatendida.*

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Introduction

Paracoccidioidomycosis (PCM) is a systemic granulomatous infection caused by the thermodimorphic fungus of the genus *Paracoccidioides*.[1-4] It is endemic in Latin America, with most cases reported in rural areas of Brazil, Colombia, Venezuela and Argentina, and is considered by the World Health Organization to be one of the neglected tropical diseases.[1-3,5,6] Infection is usually acquired through inhalation of conidia, may remain latent for 1 or 2 decades and can give rise to one of its 2 clinical forms: acute/subacute, also known as juvenile, and chronic, which is the most frequent form and mainly affects adult men.[2-4,7,8] Early diagnosis and timely treatment reduce disabling sequelae and mortality.[1,2,6] The aim of this study was to describe the clinical and epidemiological characteristics of cases of chronic PCM managed at a public hospital in the Republic of Argentina.

Method

We conducted a retrospective descriptive observational study in patients with a microbiological diagnosis of PCM treated at the Department of Dermatology of the Hospital Interzonal General de Agudos General San Martín de La Plata, Buenos Aires, Argentina, between November 2019 and October 2022. Data were obtained from analysis of the patients' medical records.

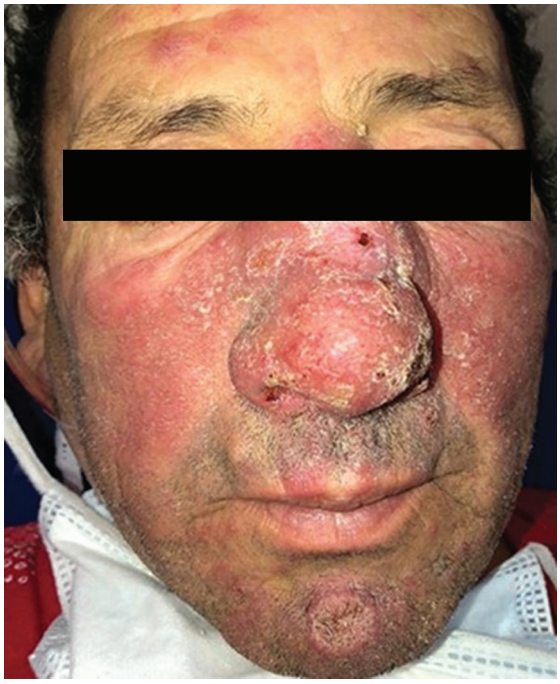

Figure 1. Infiltrated plaques on the nasal dorsum, cheeks and chin.

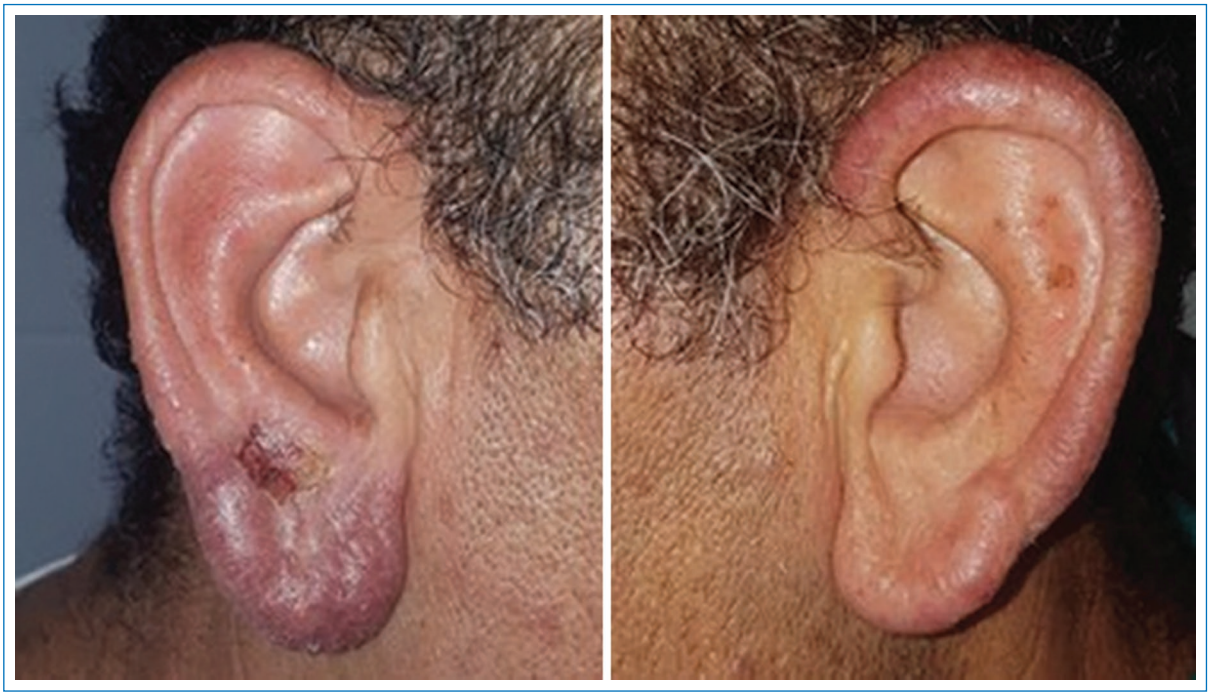

Figure 2. Infiltrated erythematous-violaceous plaques on the lobe of the right auricle and on the helix of the left auricle.

Table 1. Epidemiological, clinical, diagnostic and therapeutic characteristics of patients with PCM

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	F	M	M	M	M
Age	59	30	55	49	37
Origin	Misiones (Arg)	Chaco (Arg)	Chaco (Arg)	Bolivia	Bolivia
Past medical history	Smoker	No	Smoker	No	No
Symptom onset	2 months	2 months	12 months	8 months	4 months
Mucosal involvement	Yes	Yes	Yes	Yes	Yes
Pharyngeal	No	No	No	No	Yes
Oral	Yes	Yes	Yes	Yes	Yes
Tapir-like lip	No	Yes	No	Yes	Yes
Moriform stomatitis	Yes	Yes	Yes	Yes	Yes
Cutaneous involvement	Yes	Yes	Yes	No	No
Nasal septum	No	No	No	No	No
Direct examination	Positive	Positive	Positive	Positive	Negative
Histopathological stains	PAS +	Grocott +	PAS +	Grocott +	–
Serology	Positive	NR	Positive	Positive	NR
Culture	Positive	Positive	Positive	Positive	Positive
Systemic involvement	Yes	Yes	Yes	Yes	Yes
Lung	Yes	Yes	Yes	Yes	Yes
Adrenal glands	No	No	Yes	No	No
Spleen	No	No	No	No	Yes
Treatment	Amphotericin + itraconazole	Amphotericin + itraconazole	Amphotericin + itraconazole	Itraconazole	NT
Treatment duration, months	6	6	12	12	
Clinical course	Good	Good	Good	Good	Death

+: positive; –: negative; NR: not requested; NT: not treated; PAS: periodic acid-Schiff; smoker: tobacco smoker.

Results

Five cases of multifocal chronic PCM were included. Demographic data and clinical involvement are detailed in table 1.

The sample showed a predominance of male patients, with a male-to-female ratio of 4:1 and an age range of 30-59 years. The onset of clinical manifestations occurred a mean of 5.6 months before consultation. Cutaneous involvement presented in cases 1, 2 and 3 as infiltrated erythematous plaques in the nasal area, mental region and auricles (Figs. 1 and 2). All 5 patients had oral mucosal lesions with moriform stomatitis (Fig. 3); cases 2, 4 and 5 had tapir-like lip involvement (Fig. 4), and the patient in case 5 also had oropharyngeal ulcers. Multiple cutaneous and mucosal lesions were observed in 100% of cases. Pulmonary involvement was identified by computed tomography (CT) in all patients and described as a tree-in-bud, interstitial nodular or cavitary nodular pattern, although only 2 cases, cases 3 and 4, were symptomatic, with a dry cough. Furthermore, all patients had cervical and mediastinal lymphadenopathy. In addition, the patient in case 3 had adrenal gland hypertrophy, and the patient in case 5 had diffuse splenomegaly.

The results of the diagnostic tests requested, the treatments administered and the clinical course are

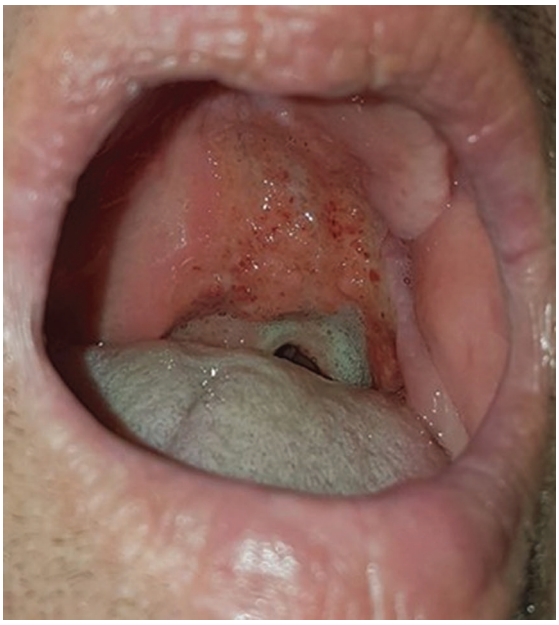

Figure 3. Moriform stomatitis on the palate.

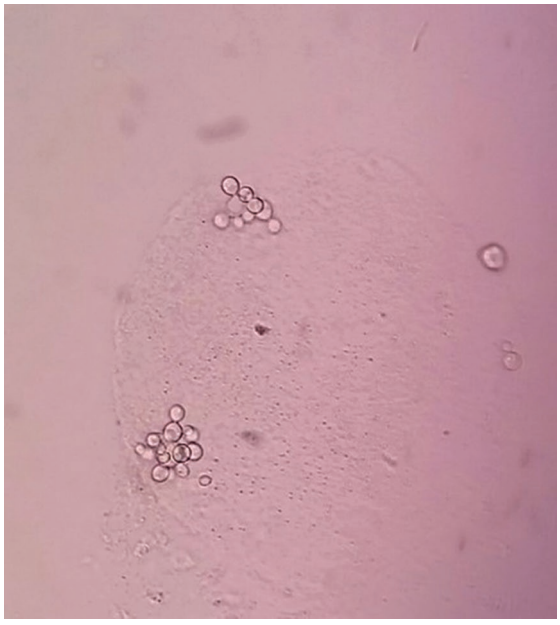

Figure 5. Direct examination showing yeasts with peripheral multibudding in a "ship's-wheel" pattern.

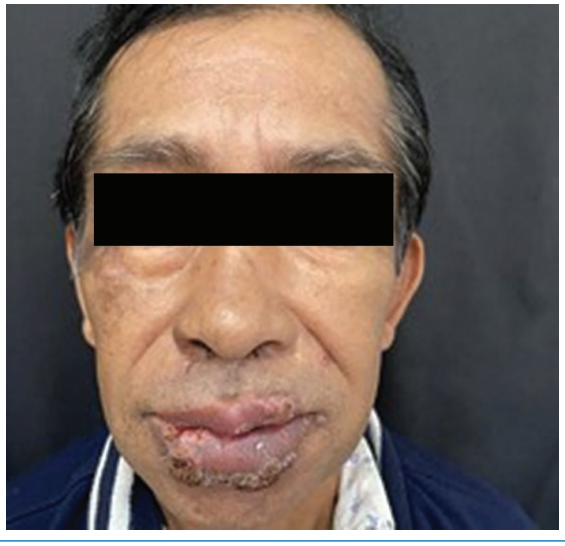

Figure 4. Tapir-like lip.

summarised in table 1. In 4 patients, cases 1, 2, 3 and 4, direct examination and histopathological stains were compatible with *Paracoccidioides* (Figs. 5 and 6), and in all reported cases the culture was positive for *Paracoccidioides* sp., without species differentiation, as molecular techniques were not available.

Regarding treatment, the patients in cases 1, 2 and 3 received IV liposomal amphotericin B for 15 days, followed by oral itraconazole for 6-12 months. The patient in case 4 received oral itraconazole from the outset, whereas the patient in case 5 did not receive treatment because the culture was positive for *Paracoccidioides* sp. post mortem.

Discussion

PCM is a disease caused by species of the fungus *Paracoccidioides*: *brasiliensis* and *lutzii*. The first reported case was described in 1908 in São Paulo, Brazil, by Adolpho Lutz.[2,4,5] *Paracoccidioides* is a thermodimorphic fungus that develops in nature at 28 °C as a septate hyaline mycelium with conidia known as propagules. In cultures at 35-37 °C or in host tissues, the propagules transform into characteristically multibudding yeasts of variable size, 4-40 μm.[2,5,6,9] It grows in the soil of humid environments at temperatures between 17 and 24 °C, with high rainfall rates, 800-2,000 mm/year; therefore, endemic areas correspond to tropical and subtropical regions of Latin America, where Brazil accounts for 80% of cases.[3-6,9] In Argentina, there are 2 well-defined endemic areas: the northwestern provinces, Tucumán, Salta and Jujuy, and the northeastern provinces, Chaco, Corrientes, Misiones and Formosa.[1,2] In our sample, the patients in cases 4 and 5 were from Bolivia, whereas cases 2 and 3 were from the province of Chaco and the patient in case 1 was from Misiones. Because of its prolonged

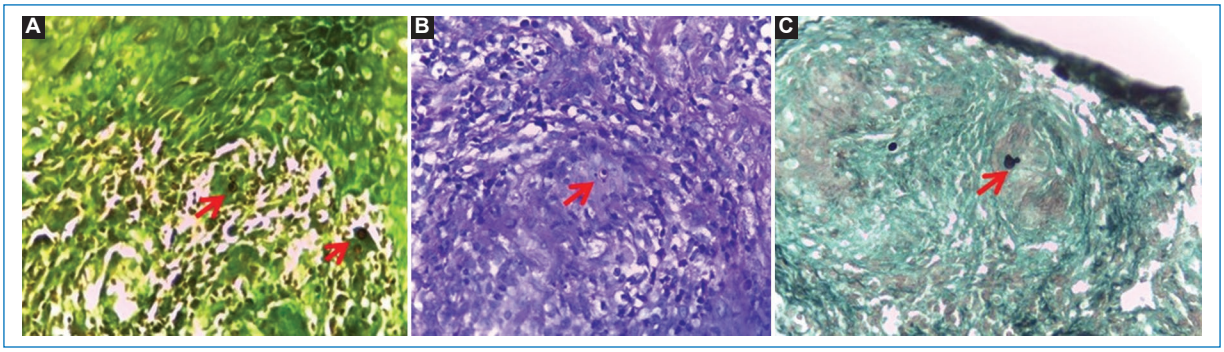

Figure 6. A: grocott stain (40X). **B:** periodic acid-Schiff (PAS) stain (40X). C: Grocott stain with silver impregnation technique (40X).

latency phase, most cases are diagnosed far from the endemic area, as occurred in case 3 of our series, who developed clinical signs of the disease 35 years after moving from his place of origin. The incidence data for PCM are not well known because it is not a notifiable disease in the health system.[1,3-7]

Fungus has been isolated from humid soils, armadillos, domestic animals, horses, monkeys and sheep; therefore, it may be considered an occupational disease, particularly among rural workers.[1,3-6]

The main risk factors are smoking, alcoholism, immunosuppression and malnutrition.[2] The patients in cases 1 and 3 were smokers. The disease mainly affects men, with a male-to-female ratio of 22:1.[2,5,6] The low incidence in women is believed to be due to the protective effect of the hormone 17β-estradiol, which interferes with the transformation from conidium to yeast, a necessary step for the onset of infection.[2,7] In our series, the only female patient was the patient in case 1, who was postmenopausal, supporting this theory.

Infection is mainly acquired through inhalation of airborne conidia during the first 2 decades of life and may remain latent in pulmonary lesions and lymph nodes for many years.[2,5,7,9] Active disease occurs when the fungus-host balance is disrupted.[2-5]

The clinical forms of *Paracoccidioides* sp. infection can be classified as acute/subacute, or juvenile, and chronic, or adult.[6] The first form, which accounts for 5-25% of cases, is more frequent in specific endemic areas, as occurs in the northwest of Argentina.[1] It mainly affects children, adolescents and patients with severe immunosuppression, with no sex distinction.[1,2,4,9] The onset of signs and symptoms is rapid, with a mean of 2 months, and is characterised by marked involvement of the reticuloendothelial system, with lymphadenopathy and/or hepatosplenomegaly, which frequently leads to death.[5,6] Peripheral eosinophilia is characteristic and is present in 30-50% of cases.[4,5] Mucosal and pulmonary involvement is rare, occurring in 20% and 10% of cases, respectively.[5] Of note, no patient with this clinical variant was observed in the present sample.

By contrast, the chronic form is the most frequent form of PCM, accounting for > 80% of cases, and commonly occurs in male patients aged 30-60 years, with multifocal involvement.[2,3,5,6] Symptoms are usually present for 4-6 months before consultation, and cutaneous involvement is often the reason for consultation, a finding consistent with our case series.[5,6]

The lung is the most frequently affected organ, 90%, because it is the portal of entry for *Paracoccidioides* sp.[5,6] Most patients usually report progressive dyspnoea, cough, 57%, and haemoptysis, 11%, although pulmonary involvement may be asymptomatic with a normal physical examination in 43% of cases.[5] All patients in our series had pulmonary involvement on CT, but only 2 cases had a nonproductive cough.

Lesions of the upper airway are present in 80% of cases.[7] The most widely involved organ is the larynx, followed by the oropharynx, hypopharynx and oral cavity. Involvement is bilateral, and in the oral cavity it affects the hard palate, soft palate, lips and gums, often causing tooth loss and giving the mouth an appearance similar to that of a tapir, also known as tapir-like lip.[7,8,10] Of note, the patients in cases 2, 4 and 5 presented this clinical sign. The most frequent symptoms are hoarseness, dysphagia, sialorrhoea and dyspnoea.[5,7] Typically, the oral cavity lesion is a painful granulomatous ulceration with haemorrhagic puncta, known as moriform stomatitis, as observed in all patients in our series.[5,7,10] This finding is highly suggestive, although not pathognomonic, of *Paracoccidioides* sp. infection.[5]

Cutaneous involvement is also very frequent and highly pleomorphic. Lesions may appear as plaques, papules, nodules, verrucous lesions or abscesses and may be located anywhere on the integument, although they most commonly involve the face and rarely affect the genitals, palms or soles.[5,8] In our series, cases 1, 2 and 3 had painless infiltrated plaques in the nasal area, mental region and auricles.

The adrenal glands are the third most frequently involved organ. Up to 40% of cases show CT abnormalities, with irregular borders and changes in volume and/or density.[5,8] This may be asymptomatic or associated with symptoms of adrenal insufficiency, such as anorexia, weight loss, fatigue, arterial hypotension, nausea or vomiting, and ionic abnormalities, such as hyperkalaemia and hyponatraemia.[5,10] In only 1 patient in our series, case 3, CT showed asymptomatic involvement of both adrenal glands.

Other organs that may be less frequently affected include the digestive system, bones and joints, kidneys, central nervous system, eyes and male reproductive system.[2,5,10]

Of note, there are no differences in the clinical signs of PCM caused by *P. brasiliensis* and *P. lutzii*, although the latter is associated with a worse prognosis.[5]

For the diagnosis of disease caused by *Paracoccidioides* sp., direct observation of the fungus in a fresh preparation with 10% potassium hydroxide or calcofluor has a sensitivity of 85%-100%, depending on the type of sample, its processing and the clinical form.[9] Samples may consist of sputum, scraping of cutaneous lesions or secretions.[8,10] These preparations show the pathognomonic extracellular thick-walled multibudding yeasts arranged around a mother cell, known as a ship's-wheel pattern, or, when there are 2 polar buds, a Mickey Mouse appearance, which is suggestive but not pathognomonic of PCM.[2,5,10,11] In our series, multibudding yeasts were visualised in cases 1, 2, 3 and 4.

On histopathological examination of cutaneous lesions, depending on the patient's immune status, granulomas may be observed with or without central suppuration, together with an infiltrate composed of lymphocytes, plasma cells and eosinophils. Fungal structures may be identified using Grocott-Gomori methenamine silver or periodic acid-Schiff (PAS) staining.[4,5,9]

The definitive diagnosis of PCM requires identification of the aetiological agent by culture on selective agar media for pathogenic fungi and Sabouraud agar at room temperature, between 20 and 25 °C, followed by conversion to yeast at 35-37 °C. This method has a sensitivity of 85% when more than 1 sample is available, and growth occurs 20-30 days after culture because the fungus is slow-growing.[4,5,9] The morphology of *P. brasiliensis* and *P. lutzii* cannot be distinguished by culture; therefore, molecular techniques, such as polymerase chain reaction, are required.[6,11]

In our patients, the diagnosis was reached through positive culture for *Paracoccidioides*, but molecular techniques for species differentiation were not available.

Serological tests are useful for diagnosis and treatment follow-up because titres correlate with the severity of the clinical forms.[2,9] A positive result is highly specific and has a high positive predictive value for *Paracoccidioides* sp. infection.[9] Nevertheless, antibody detection depends on immune competence; therefore, false-negative results may occur in patients with human immunodeficiency virus infection at the AIDS stage and in patients with less than 21 days from symptom onset.[2,6] Of note, the preparations are made with *P. brasiliensis* antigens, so sensitivity is low for *P. lutzii* infection.[6] Agar gel immunodiffusion (AGID) is the most widely used method because it is simple and cost-effective, with sensitivity > 80% and specificity > 90%.[2,5,6]

The differential diagnoses of mucocutaneous signs include leishmaniasis, tuberculosis, leprosy, syphilis and other fungal diseases, such as histoplasmosis and sporotrichosis. Noninfectious diseases, such as sarcoidosis, squamous cell carcinoma, T/NK-cell non-Hodgkin lymphoma and vasculitis, should also be considered.[3,5,6,8,10] Table 2 illustrates the clinical characteristics and diagnostic clues of the main differential diagnoses.

Unlike other fungi, *Paracoccidioides* sp. is susceptible to most antifungal agents. The most widely used agents in clinical practice are itraconazole and amphotericin B. The use of antibiotics such as trimethoprim (TMP)/sulfamethoxazole (SMX) has also been described.[5,6,9] There is currently no evidence of resistance to these drugs.[6]

Hospitalisation for IV treatment is indicated in patients with disseminated clinical forms with complications such as respiratory failure, neurological abnormalities or adrenal insufficiency, or with associated comorbidities such as HIV infection or TB.[6] Amphotericin B should be administered for the shortest possible time, with an average of 2-4 weeks, either as deoxycholate or lipid formulations, until clinical stability is achieved.[5,6,9] The induction dose of

Table 2. Differential diagnoses of chronic PCM

Condition	Clinical features	Systemic involvement	HP	Diagnostic clues
Chronic PCM	Moriform stomatitis, tapir-like lip	Pulmonary, lymph node and adrenal involvement	Granulomatous dermatitis, multibudding yeasts, "ship's- wheel" pattern	Rural epidemiology; characteristic mucosal involvement; multibudding yeasts
Mucocutaneous leishmaniasis	Destructive naso-oral ulcers affecting the hard palate, "espundia cross"	Usually absent or limited	Granulomas with macrophages and amastigotes	History of insect bite; absence of pulmonary involvement
Cutaneous tuberculosis	Very painful chronic ulcers, orificial TB; plaques and tubercles, lupus vulgaris	Pulmonary and extrapulmonary, e.g., lymph node, gastrointestinal	Epithelioid granulomas with caseous necrosis	Caseous necrosis; AFB; response to antituberculous treatment
Chronic disseminated histoplasmosis	Poorly infiltrated oral or cutaneous ulcers	Pulmonary, hepatosplenic and bone marrow involvement	Small intracellular yeasts within macrophages	Small yeasts without multibudding; frequent in immunocompromised patients
Squamous cell carcinoma	Indurated, infiltrative ulcer, progressive growth; bleeding	Local and lymph node involvement	Proliferation of atypical keratinocytes with keratin pearls	Absence of granulomas; marked cellular atypia; no response to antifungals

AFB: acid-fast bacilli; HP: histopathology; PCM: paracoccidioidomycosis; TB: tuberculosis.

amphotericin B deoxycholate is 0.5-0.7 mg/kg/day, maximum 50 mg/day, and the dose for lipid formulations is 3-5 mg/kg/day. An alternative to intravenous treatment is TMP/SMX at a dose of 800 mg/160 mg every 8 hours.[6]

Mild or moderate forms and the consolidation phase after IV treatment may be managed on an outpatient basis, and itraconazole at a dose of 200 mg/day is recommended until cure is achieved, usually between 9 and 18 months, with a mean of 12 months.[6,12]

The criteria for cure of PCM may be clinical, radiological and immunological.[9] The clinical criteria refer to remission and healing of clinical signs, whereas radiological criteria refer to stabilisation of established lesions, fibrotic and/or emphysematous scars and absence of new infiltrates demonstrated by imaging methods such as CT. Finally, the immunological criterion requires a decrease in complement fixation titres to levels considered residual or cicatricial, 1:8-1:16, and stabilisation in 2 samples: one 6 months after treatment initiation and another at treatment completion.[9]

When serological testing cannot be performed, as in the present series, treatment with itraconazole is recommended for 6-9 months in mild cases and for 12-18 months in moderate to severe cases.[5]

Cutaneous and mucosal lesions are the first to respond to antifungal treatment, after approximately 30 days. Regression of lymphadenopathy follows within 45-90 days, whereas stabilisation of radiological findings is observed 6 months after treatment initiation.[6]

Conclusions

The importance of clinical suspicion of *Paracoccidioides* sp. infection should be emphasised in the presence of extensive mucocutaneous involvement, as should scraping of lesions for direct observation in order to initiate antifungal treatment early and reduce morbidity and mortality.

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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 on humans or animals were performed for this research.

Confidentiality, informed consent and ethical approval. The authors obtained approval from the

Ethics Committee for the analysis of routinely collected and anonymised clinical data. Owing to the nature of the study, individual informed consent was not required. The relevant ethical recommendations were followed.

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