European Journal of Pain

REVIEW ARTICLE OPEN ACCESS

Pain Management in Erythromelalgia: A Systematic Review and Graded Appraisal Across Etiological Subtypes

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Received: 2 July 2026 | **Revised:** 2 August 2026 | **Accepted:** 17 August 2026

ABSTRACT

Introduction: Erythromelalgia is a rare disorder characterised by burning pain, erythema and increased skin temperature in the extremities. Its pathophysiological heterogeneity, together with variable treatment responses, complicates management in the absence of evidence-based guidelines. This systematic review appraised pain-management strategies across reported aetiological subtypes.

Databases and Data Treatment: Following PRISMA 2020 guidelines, the review was registered in PROSPERO (CRD420251232074). PubMed, Embase, the Cochrane Library and ClinicalTrials.gov were searched for studies published or registered between 1 January 2000 and 30 April 2026. Randomised controlled trials, non-randomised interventional studies, cohort studies and case series were eligible; non-randomised studies required at least five individuals. Risk of bias was assessed using Joanna Briggs Institute tools and certainty of evidence using GRADE.

Results: Of 3372 records, 25 studies reporting 591 individuals were included. Aetiological subtype was reported for 277 individuals (46.9%). Mechanistic and aetiological characterisation varied substantially across domains, with haematological data available for 72.6% and *SCN9A* status for 19.0% of the overall population. Moderate-certainty evidence supported aspirin in myeloproliferative neoplasm-associated erythromelalgia. Low-certainty evidence suggested benefit from mexiletine and carbamazepine in primary erythromelalgia, as well as from prostaglandin analogues, corticosteroids, selected topical therapies and sympathetic interventions in specific contexts. Evidence for selective $Na_v1.7$ inhibitors and most other interventions was of very low certainty.

Conclusions: Treatment-response patterns in better-characterised populations suggest that aetiology and underlying mechanisms may be relevant to treatment selection. However, this mechanism-informed approach remains hypothesis-generating and requires prospective validation through systematic aetiological and mechanistic characterisation.

Significance Statement: This systematic review provides a comprehensive, graded evaluation of the full spectrum of pain-management strategies in erythromelalgia, including systemic, topical, interventional and non-pharmacological approaches, across reported aetiological subtypes. Integrating risk-of-bias appraisal and GRADE certainty ratings, it identifies moderate-certainty evidence for aspirin in myeloproliferative neoplasm-associated disease and low-certainty evidence for conventional sodium-channel blockers in selected primary forms, while evidence for other interventions remains low or very low. These patterns suggest that aetiology may inform treatment selection, but require prospective validation.

1 | Introduction

Erythromelalgia is a rare disorder characterised by recurrent episodes of severe burning pain, erythema and increased skin temperature, predominantly affecting the distal extremities (Caldito et al. 2024). Although the term *erythermalgia* has historically been used, *erythromelalgia* is now the preferred terminology in clinical practice and research, as it encompasses the full spectrum of inherited and acquired forms of the disorder (Michiels et al. 1995; Mann et al. 2019).

The clinical presentation of erythromelalgia varies between individuals, particularly in the number and anatomical distribution of affected sites and the frequency of attacks. Symptoms are typically triggered or exacerbated by heat exposure and physical activity and are often relieved by cooling. Severe or refractory forms may result in substantial functional impairment and cutaneous complications, most commonly related to excessive or prolonged cooling used as a coping strategy (Caldito et al. 2024).

Diagnosis is primarily clinical and relies on recognition of the characteristic triad of burning pain, erythema and increased skin temperature occurring in a typical episodic pattern. No objective diagnostic test or validated laboratory marker is currently available, and clinical signs are frequently absent between attacks (Caldito et al. 2024). Several symptom-based diagnostic criteria have been proposed; however, none have been formally validated (Eaton and Mayrovitz 2025).

From an aetiological perspective, erythromelalgia is commonly classified as primary or secondary according to the presence of an identifiable underlying condition. Primary erythromelalgia, estimated to affect fewer than 2 per 100,000 individuals, comprises both genetic and idiopathic forms (Tang et al. 2015). Pathogenic gain-of-function variants in *SCN9A*, which encodes $Na_v1.7$, represent the best-established genetic cause. These variants alter channel activation and inactivation, lowering the threshold for action potential generation and promoting repetitive firing in peripheral nociceptive neurons (Dib-Hajj et al. 2005, 2013). Idiopathic erythromelalgia is defined by the absence of an identifiable genetic cause or underlying condition.

Secondary erythromelalgia occurs in association with an identifiable condition or exposure, most characteristically myeloproliferative neoplasms, but also peripheral neuropathies, autoimmune or inflammatory diseases, metabolic, neurological and vascular disorders, as well as certain medications or toxins (Mann et al. 2019; Caldito et al. 2024). Although clinically useful, this aetiological classification does not fully capture the underlying pathophysiology of erythromelalgia, and whether aetiological subtype can help predict treatment response remains uncertain (Tham and Giles 2018; Caldito et al. 2024).

Management of erythromelalgia remains challenging because of marked interindividual variability in treatment response, the absence of evidence-based treatment guidelines and substantial heterogeneity in therapeutic approaches across clinical practice and the published literature (Tham and Giles 2018). Previous narrative reviews have addressed medical management and procedural interventions separately (Ma et al. 2023; Lee et al. 2024). More recently, Algarni et al. (2025) conducted a systematic review of treatment efficacy and tolerability; however, only six studies were included, providing a limited representation of the range of therapeutic approaches reported in the literature.

To our knowledge, no previous systematic review has comprehensively assessed the full range of systemic pharmacological, topical, interventional and non-pharmacological pain-management strategies or evaluated the certainty of evidence across treatment categories. The present review was therefore undertaken to address these gaps through a comprehensive synthesis and GRADE-based appraisal of the available evidence. A secondary objective was to explore whether reported treatment responses varied according to aetiological subtype and underlying pathophysiological mechanisms.

2 | Methods

2.1 | Protocol and Registration

The review protocol was prospectively registered in PROSPERO on 21 November 2025. The full protocol is publicly available at https://doi.org/10.17504/protocols.io.14egnrqjml5d/v1 and was developed by the Pain & Rare Diseases Working Group of the French Pain Society (SFETD).

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al. 2021).

2.2 | Eligibility Criteria

Studies were eligible if they met all of the following criteria:

- Randomised controlled trials (RCTs), non-randomised interventional studies, prospective or retrospective cohort studies, or case series;
- Inclusion of participants diagnosed with erythromelalgia, Regardless of age;
- Reporting of outcomes relevant to pain management.

Non-randomised studies were required to include at least five participants. No minimum sample size was imposed for RCTs because random allocation and the presence of a comparator provided an internal basis for estimating treatment effects. However, very small trials were considered highly imprecise, and sample size was taken into account when interpreting the findings and assessing the certainty of evidence.

Similarly, no minimum treatment duration or follow-up period was required for eligibility, although both were considered in these assessments.

Studies were excluded if they were case reports or other non-randomised studies involving fewer than five participants;

reviews, editorials or letters; conference abstracts or posters without a corresponding full-text publication; or animal or in vitro studies.

2.3 | Information Sources

A systematic literature search was conducted in PubMed (MEDLINE), Embase, the Cochrane Library and ClinicalTrials.gov to identify relevant studies. The search covered the period from 1 January 2000 to 30 April 2026. Studies published in languages other than English or French were excluded when an adequate translation was unavailable.

2.4 | Search Strategy

Database-specific search strategies were developed for each database using controlled vocabulary terms (MeSH and Emtree) and free-text keywords related to erythromelalgia and pain management. Boolean operators were applied as appropriate to maximise retrieval of relevant records.

The complete electronic search strategies for each database are provided in Appendix S1.

2.5 | Study Selection

All retrieved records were imported into Rayyan (Ouzzani et al. 2016) for duplicate detection and management of the study-selection process. Titles and abstracts were independently screened by two reviewers (C.R. and S.B.) according to predefined eligibility criteria. Full-text articles were then retrieved and independently assessed for all potentially eligible studies. Disagreements were resolved by consensus, with arbitration by a third reviewer (J.F.) when necessary.

2.6 | Data Extraction

Data were independently extracted by two reviewers (C.R. and M.L.) using predefined extraction forms, with discrepancies resolved by consensus or, when necessary, through adjudication by a third reviewer (J.F.). Extracted variables included study characteristics (authors, year, country and study design), population characteristics (sex, sample size, age and erythromelalgia subtype), intervention details, follow-up duration, reported outcomes, adverse events and, when available, genetic, biological or pathophysiological data relevant to characterising underlying mechanisms.

For the purposes of this review, aetiological subtype was assigned according to the classification reported by the study authors and was considered separately from direct mechanistic characterisation. Cases explicitly described as primary, genetic or idiopathic were classified as primary, whereas those explicitly described as secondary or attributed to an underlying condition or exposure were classified as secondary. The presence of a comorbidity alone, without explicit causal attribution by the study authors, was considered insufficient to classify a case as secondary.

2.7 | Primary Outcome

The primary outcome was treatment response, as reported by the original study authors. Because definitions and measurement methods varied substantially across studies, no common responder threshold was imposed. When quantitative pain measures were available, changes from baseline to the latest reported follow-up were extracted. Otherwise, author-defined outcomes such as partial or complete symptom improvement, reduced attack frequency or duration or lower cooling requirements were retained.

Interpretation of the findings took into account both the clinical relevance of the reported outcomes and the study design. Between-treatment comparisons were made only when directly supported by a within-study comparator. When therapies were administered concomitantly or sequentially, the contribution of each individual treatment was considered indeterminate unless treatment-specific outcomes were explicitly reported. In such cases, observed changes were associated only with the overall therapeutic strategy and were not assigned to any individual treatment.

2.8 | Secondary Outcomes

Prespecified secondary outcomes were extracted, when available, to further characterise treatment effectiveness and safety and to explore potential underlying mechanisms. These included:

- Characteristics of pain-management strategies;
- Adverse events and treatment tolerability;
- Health-related quality-of-life measures;
- Mechanistic and aetiological data, including genetic findings and pathophysiological insights.

2.9 | Data Synthesis

Given the rarity of erythromelalgia and the anticipated heterogeneity in interventions and outcome-assessment methods, no quantitative meta-analysis was planned. Findings were synthesised narratively and organised according to study design, reported aetiological subtype, pathophysiological context and pain-management strategy. Comparisons according to aetiological subtype or underlying mechanism were undertaken only when studies reported results for clearly defined subgroups.

2.10 | Risk of Bias Assessment

Methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, selected according to study design (Munn et al. 2020; Tufanaru et al. 2020; Barker et al. 2023, 2025). Two reviewers (M.L. and I.D.) independently performed the assessments, with disagreements resolved through discussion or, when necessary, adjudication by a third reviewer (C.R.).

Based on JBI appraisal domains, studies were categorised as having low, moderate or high risk of bias. Risk-of-bias assessments were not used to determine study eligibility but were considered when interpreting the findings.

2.11 | Certainty of Evidence

The certainty of the evidence for key outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt et al. 2011; Balshem et al. 2011). The evidence was evaluated across the five standard GRADE domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.

Consistent with methodological guidance for rare diseases, the rarity of erythromelalgia was taken into account when interpreting the limited volume of available evidence, while the standard GRADE criteria were applied without modification (Pai et al. 2015, 2019).

3 | Results

3.1 | Study Selection and Characteristics

The search identified 3372 records, of which 1487 were duplicates. After title and abstract screening and full-text assessment, 25 studies met the inclusion criteria (Figure 1).

The 25 included studies reported a total of 591 individuals. Study designs comprised eight randomised controlled trials (32.0% of studies; $n = 106$), one non-randomised placebo-controlled crossover trial (4.0%; $n = 21$), three prospective single-arm interventional studies (12.0%; $n = 29$), two prospective cohort studies (8.0%; $n = 43$) and 11 retrospective case series (44.0%;

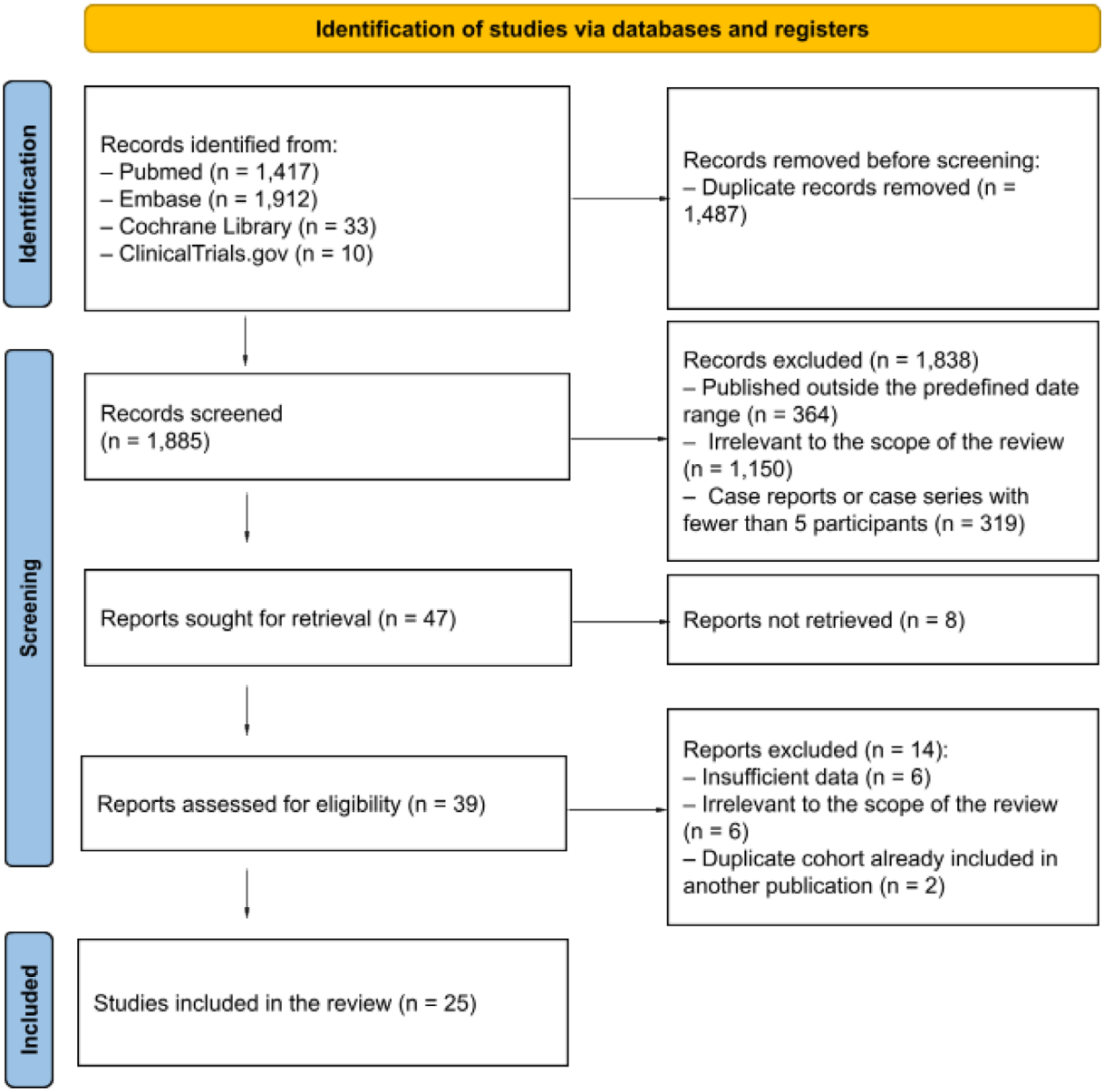

FIGURE 1 | PRISMA flow diagram.

$n = 392$). The studies were published between March 2000 and December 2025.

Primary erythromelalgia was reported in 129 individuals (21.8%) and secondary erythromelalgia in 148 (25.0%), while the subtype was unspecified in 314 (53.1%). Mixed-age populations accounted for 43.8% of individuals ($n = 259$), adult-only populations for 43.7% ($n = 258$) and paediatric-only populations for 12.5% ($n = 74$).

3.2 | Interventions

Interventions were heterogeneous and included systemic pharmacological, topical, interventional and non-pharmacological approaches.

Systemic therapies were evaluated in 18 of the 25 included studies. These included platelet-targeted therapies, namely aspirin and anagrelide (Michiels et al. 2003, 2006; Cacciola et al. 2005; Rocca et al. 2024); prostaglandin analogues, including iloprost and misoprostol (Kalgaard et al. 2003; Mørk et al. 2004); corticosteroids (Cook-Norris et al. 2012; Pagani-Estévez et al. 2017; Davis et al. 2000; Akabane et al. 2022; Sun et al. 2023); sodium-channel blockers, mainly mexiletine and carbamazepine (Davis et al. 2000; Fischer et al. 2009; Geha et al. 2016; Akabane et al. 2022; Wang et al. 2022; Michelerio et al. 2023; Sun et al. 2023); and selective $Na_v1.7$ inhibitors, including PF-05089771 and oral XPF-002 (Goldberg et al. 2012; Cao et al. 2016; Pfizer 2019). Additional systemic therapies assessed within multimodal or exploratory treatment strategies included gabapentin, antidepressants, antihistamines, magnesium supplementation, interferon-α-2b and intravenous immunoglobulins (Davis et al. 2000; Cook-Norris et al. 2012; Huang et al. 2014; Akabane et al. 2022; Sun et al. 2023).

Topical therapies were evaluated as primary interventions in four studies and included amitriptyline–ketamine combinations (Poterucha et al. 2013), topical amitriptyline monotherapy (AlgoTherapeutix 2025), mepyramine (Ducrocq et al. 2025) and the selective $Na_v1.7$ inhibitor XPF-002 (Xenon Pharmaceuticals 2014). Additional topical agents, particularly lidocaine-based formulations, were reported as components of broader multimodal treatment strategies (Davis et al. 2000; Sun et al. 2023).

Non-pharmacological strategies were evaluated in three studies and included physical methods and multidisciplinary pain rehabilitation programmes (Davis et al. 2000; Durosaro et al. 2008; Cook-Norris et al. 2012). Interventional approaches included chemical lumbar sympathectomy and other sympathetic procedures evaluated in refractory erythromelalgia (Davis et al. 2000; Cook-Norris et al. 2012; Wang et al. 2018).

Study characteristics and interventions are summarised in Tables 1 and 2 for interventional and observational studies, respectively.

3.3 | Risk of Bias

Overall methodological quality varied according to study design, as assessed using the Joanna Briggs Institute (JBI) Critical Appraisal tools (Munn et al. 2020; Tufanaru et al. 2020; Barker et al. 2023, 2025).

Among the eight randomised controlled trials, five were judged to have a low risk of bias (Kalgaard et al. 2003; Goldberg et al. 2012; Geha et al. 2016; Pfizer 2019; AlgoTherapeutix 2025), whereas three were judged to have a moderate risk of bias, mainly because of treatment-arm imbalance and limited comparative outcome reporting in one trial (Xenon Pharmaceuticals 2014), exploratory efficacy assessment with limited endpoint hierarchy in another (Cao et al. 2016) and open-label treatment allocation in the third (Rocca et al. 2024).

The single non-randomised placebo-controlled fixed-sequence crossover trial was judged to have a moderate risk of bias (Mørk et al. 2004). Although the fixed treatment sequence, with placebo followed by misoprostol, was intended to minimise potential carry-over effects, the absence of randomisation remained an important methodological limitation despite double blinding and standardised outcome assessment.

All prospective single-arm interventional studies were judged to have a moderate risk of bias because they lacked comparator groups, despite prospective data collection and predefined treatment protocols (Cacciola et al. 2005; Wang et al. 2018, 2022). The prospective cohort studies were also judged to be at moderate risk of bias because they were non-randomised and open-label, with limited control for confounding (Huang et al. 2014; Michiels et al. 2006).

Most retrospective case series were judged to have a moderate risk of bias (Michiels et al. 2003; Durosaro et al. 2008; Fischer et al. 2009; Poterucha et al. 2013; Pagani-Estévez et al. 2017; Akabane et al. 2022; Michelerio et al. 2023; Sun et al. 2023; Ducrocq et al. 2025), reflecting referral-centre recruitment, heterogeneous therapeutic exposure, retrospective outcome ascertainment and the absence of comparator groups. Two retrospective case series were judged to have a high risk of bias (Davis et al. 2000; Cook-Norris et al. 2012) because they combined substantial population heterogeneity, absence of disease-subtype stratification, highly heterogeneous therapeutic exposure and retrospective outcome ascertainment, substantially limiting attribution of treatment effects.

Detailed study-level risk-of-bias assessments are provided in Appendix S2.

3.4 | Primary Outcome

Treatment effects were heterogeneous across studies and interventions.

3.4.1 | Systemic Pharmacological Treatments

Sodium-channel blockers were evaluated predominantly in small cohorts of individuals with primary erythromelalgia. In this population, mexiletine and carbamazepine were repeatedly associated with reductions in pain intensity and overall attack burden (Fischer et al. 2009; Geha et al. 2016; Wang

TABLE 1 | Characteristics of interventional studies evaluating therapeutic efficacy in erythromelalgia[a].

First author (year)	Country	Study design	Population	Type of erythromelalgia[b]	Age[c]	Main study focus	Treatment protocol	Effect on erythromelalgia
Kalgaard et al. (2003)	Norway	Randomised, double-blind, placebo-controlled trial	Adolescent and adult individuals with primary erythromelalgia localised to the feet. Skin microvascular perfusion and sympathetic vasoconstrictor function were assessed by laser Doppler flowmetry during Valsalva's manoeuvre and contralateral cooling, with baseline responses consistent with sympathetic dysfunction. No genetic or neuropathic characterisation was reported.	Primary ($n = 12$)	52 [17–74]	To assess the efficacy and safety of an intravenous prostaglandin analogue on pain-related symptoms and sympathetic dysfunction in primary erythromelalgia.	Intravenous iloprost infused for 6 h/day for 3 consecutive days (10–40 mL/h); placebo: 0.9% NaCl.	No statistically significant differences were observed between the iloprost and placebo groups. Median cooling requirements decreased from 2.8 (1.9–4.0) to 1.9 (0.1–3.0) in the iloprost group, compared with 1.8 (0.4–3.6) to 1.2 (0.0–2.4) in the placebo group. However, the reduction from baseline reached statistical significance only within the iloprost group ($p < 0.05$).
Mørk et al. (2004)	Sweden, Norway	Non-randomised, double-blind, placebo-controlled crossover trial	Adult individuals with erythromelalgia. Reported comorbidities included connective-tissue disease in 3 individuals (14%), myeloproliferative disease in 2 (10%), diabetes mellitus in 2 (10%) and sciatica in 2 (10%). Microvascular testing showed an exaggerated heat-induced increase in skin perfusion with reduced capillary density and increased intercapillary distance, supporting arteriovenous shunting and impaired nutritive perfusion.	Primary ($n = 12$); Secondary ($n = 9$)	47 [21–60]	To evaluate the efficacy and safety of an oral prostaglandin analogue on pain-related symptoms and sympathetic dysfunction in erythromelalgia.	Misoprostol (0.4–0.8 mg/day) vs. placebo, each for 6 weeks.	Misoprostol significantly reduced pain intensity (VAS) and cooling requirements after 6 weeks of treatment compared with placebo (both $p < 0.01$). Fourteen of 21 individuals achieved a ≥ 20% reduction in pain with misoprostol compared with 4 of 21 with placebo ($p < 0.05$). The clinical benefit was not maintained 3 months after treatment discontinuation.
Cacciola et al. (2005)	Italy	Prospective single-arm interventional study	Adult individuals with essential thrombocythaemia, including an erythromelalgia subgroup. Elevated platelet, coagulation, fibrinolysis and endothelial activation markers in the overall cohort supported a platelet-mediated microvascular mechanism.	Secondary ($n = 9$)	48 [24–72]	To evaluate the effect of anagrelide on thrombocythaemia-related symptoms, including erythromelalgia.	Anagrelide was initiated at 0.5 mg/day and titrated weekly to achieve a platelet count $< 500 \times 10^9$/L.	Anagrelide was associated with a complete resolution of erythromelalgia after achievement of a sustained platelet response ($< 500 \times 10^9$/L for > 1 month), associated with normalisation of platelet activation markers (PF4 118 to 8.5 IU/mL) and endothelial dysfunction markers (TFPI 166 to 98 ng/mL).

(Continues)

TABLE 1 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[b]	Age[c]	Main study focus	Treatment protocol	Effect on erythromelalgia
Goldberg et al. (2012)	Canada	Randomised, double-blind, placebo-controlled crossover trial	Adult individuals with primary erythromelalgia carrying pathogenic *SCN9A* variants.	Primary ($n=4$)	37 [24–46]	To explore the effect of an oral selective $Na_v1.7$ inhibitor in primary erythromelalgia.	Oral XPF-002 (800 mg/day) or placebo for 2 days, separated by a 2-day washout; pain induced by heat or physical activity if not spontaneous.	XPF-002 attenuated experimentally induced pain during the 2-day treatment period, with delayed induction of maximal pain and a 42% reduction in post-induction pain intensity during the subsequent 2 h compared with placebo (95% CI 13%–71%; $p=0.014$).
Xenon Pharmaceuticals (2014)	United States	Randomised, double-blind, placebo-controlled parallel-group study	Adult individuals with primary erythromelalgia and episodic pain affecting the hands or feet.	Primary ($n=8$)	44.4 (22.2)	To assess efficacy and safety of a topical selective $Na_v1.7$ inhibitor in primary erythromelalgia.	Topical XPF-002 8% or placebo applied twice daily for 14–21 days.	Topical XPF-002 reduced cooling requirements during treatment days 14–21, reflected by fewer cooling episodes (0.24/day [0.03–0.27] vs. 2.4/day with placebo) and shorter cooling duration (7.8 min/day [0–13.3] vs. 86 min/day with placebo). However, interpretation was substantially limited by the marked treatment-group imbalance, with seven individuals receiving XPF-002 and only one receiving placebo.
Geha et al. (2016)	United States	Randomised, double-blind, placebo-controlled crossover trial	Adult individuals with inherited erythromelalgia associated with the pathogenic *SCN9A* p.Ser241Thr variant.	Primary ($n=2$)	NR	To characterise pain-related brain network activity using fMRI and compare pain outcomes after carbamazepine vs. placebo in primary erythromelalgia.	Carbamazepine titrated from 400 to 1600 mg/day with 2-week maintenance; placebo matched.	Carbamazepine reduced time spent in pain during the 15-day maintenance period, with mean daily pain duration decreasing from 424 to 231.9 min/day in Patient 1 and from 61 to 9.1 min/day in Patient 2 compared with placebo. Mean pain episode duration was also reduced (615 to 274.1 min and 91.5 to 45.3 min, respectively), accompanied by changes in pain-related cerebral activity on fMRI.
Cao et al. (2016)	United Kingdom	Randomised, double-blind, placebo-controlled crossover trial	Adult individuals with inherited erythromelalgia, with pathogenic *SCN9A* variants.	Primary ($n=5$)	40.2 (NR)	To evaluate the clinical efficacy of an oral selective $Na_v1.7$ inhibitor in inherited erythromelalgia.	Single oral dose of PF-05089771 (1600 mg) or placebo in a crossover design; heat-evoked pain attacks induced before and after dosing during two treatment sessions.	PF-05089771 reduced heat-evoked maximum pain scores 4–9 h after a single dose, with treatment differences versus placebo of −2.56 PI-NRS points at 4–5 h (90% CI, −4.74 to −0.39; $p=0.06$) and −3.63 PI-NRS points at 8–9 h (90% CI, −6.91 to −0.34; $p=0.03$).

(Continues)

TABLE 1 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[b]	Age[c]	Main study focus	Treatment protocol	Effect on erythromelalgia
Wang et al. (2018)	China	Prospective single-arm interventional study	Paediatric and adult individuals with refractory erythromelalgia, defined by failure of at least five medications and baseline pain intensity ≥ 5 on the visual analogue scale. Pathogenic *SCN9A* variants were identified in five individuals.	Primary ($n = 10$) Secondary ($n = 3$)	15 [11–52]	Evaluate short- and long-term efficacy and safety of chemical lumbar sympathectomy (CLS) in refractory erythromelalgia.	Bilateral L3–L4 chemical lumbar sympathectomy (CLS) performed under fluoroscopic guidance using 5% phenol, with 2 years follow-up.	Chemical lumbar sympathectomy was associated with a reduction in mean pain intensity from 8.2 at baseline to 1.9 after 1 week. A complete response was reported in 69.2% (9/13) of individuals and remained sustained at 2 years in 55.6% (5/9) of initial responders. Relapse occurred in 23.1% (3/13) and appeared to be more frequent among individuals with *SCN9A*-associated erythromelalgia.
Pfizer (2019)	United States	Randomised, double-blind, placebo-controlled crossover trial	Adult individuals with inherited erythromelalgia carrying pathogenic *SCN9A* variants.	Primary ($n = 5$)	40.2 (18.7)	To assess efficacy and safety of an oral selective $Na_v1.7$ inhibitor in primary erythromelalgia.	Single oral dose of PF-05089771 (1600 mg) or placebo; 3-period crossover; 72-h washout; symptoms induced by heat or physical activity.	PF-05089771 did not improve the primary endpoint compared with placebo during the first 4 h after dosing (treatment difference −0.33 PI-NRS points, 90% CI −1.17 to 0.51; $p = 0.49$). However, lower heat-evoked pain scores were observed at 4–5 h and 8–9 h post-dose (treatment differences −2.56 and −3.63 PI-NRS points, respectively; $p = 0.06$ and $p = 0.03$).
Wang et al. (2022)	China	Prospective single-arm interventional study	Paediatric and adult individuals with primary erythromelalgia carrying pathogenic *SCN9A* variants.	Primary ($n = 7$)	12 [7–22]	To assess the efficacy and safety of a stepwise treatment strategy using mexiletine, carbamazepine and rizatriptan in primary erythromelalgia.	Treatment began with patient education and mexiletine (200–600 mg/day). If pain persisted, carbamazepine was added (100–800 mg/day). For acute pain attacks, rizatriptan was used (5–10 mg, max. twice daily).	During the stepwise regimen, complete or major improvement in pain and skin symptoms was reported in all individuals. Mean pain intensity decreased from 5.3 ± 1.4 at baseline to 0.8 ± 1.1 after 12 months ($p = 0.018$), with complete pain improvement reported in 85.7% (6/7) of individuals. Because mexiletine, carbamazepine, and rizatriptan were administered sequentially, their respective contributions could not be disentangled.

(Continues)

TABLE 1 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[b]	Age[c]	Main study focus	Treatment protocol	Effect on erythromelalgia
Rocca et al. (2024)	Italy	Randomised open-label controlled trial	Adults with essential thrombocythaemia or polycythaemia vera; erythromelalgia-related pain assessed as a secondary endpoint.	Secondary ($n=57$)	61 [51–68]	To compare the efficacy of once-daily versus twice-daily low-dose aspirin on complications of myeloproliferative neoplasms, including erythromelalgia.	Aspirin 100 mg once daily vs. 100 mg twice daily; 20-month follow-up.	Twice-daily dosing was associated with lower frequency of erythromelalgia symptoms over 20 months compared with once-daily dosing. Pain episodes with NRS ≥ 2 were less frequent in the hands (19% vs. 25%) and feet (20% vs. 27%) ($p<0.001$ for both comparisons).
AlgoTherapeutix (2025)	Germany, United States	Randomised, double-blind, placebo-controlled crossover trial	Adult individuals with erythromelalgia cohort. No comorbidities or etiological, genetic, or neuropathic characterisation were reported.	Aetiological subtype not clearly stratified ($n=13$)	NR	To assess efficacy and safety of topical amitriptyline.	Amitriptyline hydrochloride 15% hydrogel vs. placebo, each for 3 weeks; 1-week washout.	Topical amitriptyline (ATX01 15%) did not significantly reduce erythromelalgia pain intensity compared with placebo after two 3-week treatment periods (mean pain attack intensity score 4.47 [95% CI 3.0–7.6] vs. 4.50 [95% CI 2.8–6.3]; $p=0.09$).

[a]When no peer-reviewed publication was available at the time of data extraction, information was obtained from the corresponding ClinicalTrials.gov record. These studies were cited using the sponsor name and year.
[b]Type of erythromelalgia was reported as defined in the original publication or based on information provided by the authors.
[c]Age was reported as median [range] or mean (standard deviation), when available. 'NR' indicates that these data were not reported.

et al. 2022; Michelerio et al. 2023). In a prospective study of seven individuals, mean pain intensity decreased from 5.3 ± 1.4 at baseline to 0.8 ± 1.1 after 12 months of a stepwise treatment regimen comprising mexiletine, carbamazepine and rizatriptan ($p=0.018$). Complete pain relief was reported in 85.7% of individuals (6/7), although the respective contribution of each treatment could not be disentangled (Wang et al. 2022).

Oral selective $Na_v1.7$ inhibitors were evaluated predominantly in small cohorts of individuals with genetically confirmed erythromelalgia. Results varied across studies, and efficacy was frequently assessed using experimentally induced heat-evoked pain rather than spontaneous pain (Goldberg et al. 2012; Cao et al. 2016; Pfizer 2019). Oral XPF-002 reduced experimentally induced pain intensity by 42% compared with placebo (Goldberg et al. 2012), whereas PF-05089771 did not meet its primary endpoint during the first 4 h after dosing. Lower mean heat-evoked pain scores than with placebo were nevertheless observed at later post-dose time points, particularly 4–5 and 8–9 h after administration (Pfizer 2019).

Prostaglandin analogues were assessed in two placebo-controlled studies involving different aetiological populations (Kalgaard et al. 2003; Mørk et al. 2004). In the study restricted to primary erythromelalgia, intravenous iloprost reduced median cooling requirements from 2.8 (1.9–4.0) to 1.9 (0.1–3.0) on an 8-point Likert scale and improved sympathetic vasoconstrictor responses (all within-group $p<0.05$). However, no statistically significant between-group differences were detected, although improvement from baseline reached significance only in the iloprost group (Kalgaard et al. 2003). In a fixed-sequence crossover study including both primary and secondary erythromelalgia, oral misoprostol significantly improved pain, cooling requirements, and global assessment compared with placebo (all $p<0.01$). A ≥ 20% reduction in pain was achieved by 66.7% (14/21) of individuals during misoprostol treatment, compared with 19.0% (4/21) during placebo treatment. However, this clinical benefit was not maintained at the 3-month follow-up after treatment discontinuation (Mørk et al. 2004).

Platelet-targeted therapies were evaluated across different aetiological contexts. In case series comprising predominantly primary or aetiologically unstratified erythromelalgia, clinical improvement with aspirin was reported in 0%–47% of treated individuals (Davis et al. 2000; Cook-Norris et al. 2012; Michelerio et al. 2023; Sun et al. 2023). By contrast, retrospective studies reported rapid symptom relief following aspirin initiation among individuals with erythromelalgia associated with myeloproliferative neoplasms (Michiels et al. 2003, 2006). Although the specific contribution of aspirin could not always be distinguished from that of concomitant cytoreductive therapies, one study also reported the return of symptoms after aspirin discontinuation, providing further support for an aspirin-related effect (Michiels et al. 2003).

Additional indirect evidence came from an open-label comparative study in which erythromelalgia pain was assessed as a secondary outcome. Twice-daily low-dose aspirin was associated with fewer pain episodes than once-daily administration, both in the hands (19% vs. 25%) and feet (20% vs. 27%; $p<0.001$ for

TABLE 2 | Characteristics of observational studies reporting treatment outcomes in erythromelalgia.

First author (year)	Country	Study design	Population	Type of erythromelalgia[a]	Age[b]	Main study focus	Treatment strategies	Effect on erythromelalgia
Davis et al. (2000)	United States	Retrospective case series	Erythromelalgia including paediatric and adult individuals. Reported characteristics and comorbidities included smoking in 84 individuals (50.0%), hypertension in 23 (13.7%), hyperlipidaemia in 19 (11.3%), diabetes mellitus in 4 (2.4%) and myeloproliferative neoplasms in 17 (10.1%). Axonal neuropathy was identified in 21 of the 54 individuals assessed (38.9%). No genetic data were reported.	Aetiological subtype not clearly stratified ($n = 168$)	60 [5–91]	To characterise clinical presentation and outcomes of erythromelalgia.	Heterogeneous treatments were reported, including aspirin ($n = 57$), nonsteroidal anti-inflammatory drugs ($n = 49$), β-blockers ($n = 40$), antihistamines ($n = 28$), physical methods ($n = 23$), immunosuppressive therapies (oral corticosteroids or plasma exchange; $n = 12$) and sympathectomy ($n = 6$).	Heterogeneous responses with symptom improvement reported in 49% of individuals treated with nonsteroidal anti-inflammatory drugs, 47% with aspirin, 42% with β-blockers, 43.5% with physical methods, 41.7% with immunosuppressive therapies, 25% with antihistamines and 50% with sympathectomy.
Michiels et al. (2003)	Netherlands	Retrospective case series	Adult individuals with thrombocythaemia-associated erythromelalgia, including primary thrombocythaemia in 13 participants (50%) and polycythaemia vera in 13 (50%).	Secondary ($n = 26$)	54 [33–74]	To assess aspirin efficacy in erythromelalgia associated with essential thrombocythaemia and polycythaemia vera.	Aspirin loading dose (500 mg), followed by maintenance (500 mg/day).	Aspirin rapidly relieved erythromelalgia pain and resolved associated inflammatory signs in all individuals; symptoms recurred after treatment discontinuation.
Michiels et al. (2006)	Netherlands	Prospective observational cohort study	Adult individuals with essential thrombocythaemia, including a subgroup with erythromelalgia.	Secondary ($n = 14$)	59 [33–76]	To evaluate the effect of low-dose aspirin on thrombocythaemia-related complications, including erythromelalgia.	Aspirin loading dose (300–500 mg), followed by maintenance (50–80 mg/day).	Aspirin provided rapid and complete relief of erythromelalgia pain and associated symptoms in all individuals; symptoms recurred after treatment discontinuation.
Durosaro et al. (2008)	United States	Retrospective case series	Individuals with erythromelalgia and pain-related functional impairment. No comorbidities or etiological, genetic, or neuropathic characterisation were reported.	Aetiological subtype not clearly stratified ($n = 8$)	43 (16.8)	To evaluate a multidisciplinary pain rehabilitation programme.	Intensive multidisciplinary rehabilitation (8 h/day for 2 weeks) with physical therapy, occupational therapy, group education.	Multidisciplinary pain rehabilitation significantly improved pain-related functioning, including pain-related interference (52.5 ± 8.7 to 39.7 ± 11.7; $p = 0.045$), life control (49.1 ± 7.8 to 57.3 ± 4.3; $p = 0.046$) and general activity (46.6 ± 4.2 to 54.0 ± 7.4; $p = 0.047$).

(Continues)

TABLE 2 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[a]	Age[b]	Main study focus	Treatment strategies	Effect on erythromelalgia
Fischer et al. (2009)	Canada	Retrospective case series with functional assays	Familial erythromelalgia including paediatric and adult individuals. All individuals carried the *SCN9A* p.Val400Met variant.	Primary ($n=5$)	NR	To explore the effect of carbamazepine in primary erythromelalgia associated with the *SCN9A* V400M variant.	Carbamazepine 600–800 mg/day.	Carbamazepine was associated with substantial pain relief in individuals carrying the SCN9A p.Val400Met variant. Functional analyses showed normalisation of altered $Na_v1.7$ channel gating and neuronal hyperexcitability.
Cook-Norris et al. (2012)	United States	Retrospective case series	Paediatric individuals with erythromelalgia. A first-degree family history of erythromelalgia was reported in 7 individuals (22%). Reported comorbidities included hypertension in 2 individuals (6%), anaemia in 2 (6%), obesity in 1 (3%), and type 1 diabetes mellitus in 1 (3%). Small-fibre neuropathy was identified in 10 of the 17 individuals assessed (59%) and vascular abnormalities in 13 of the 14 assessed (93%).	Aetiological subtype not clearly stratified ($n=32$)	14 [5–18]	To characterise paediatric erythromelalgia, with emphasis on clinical features and treatment response.	Heterogeneous treatments, including topical lidocaine ($n=14$), aspirin ($n=14$), nonsteroidal anti-inflammatory drugs ($n=14$), antidepressants ($n=10$), antihistamines ($n=8$), corticosteroids ($n=6$), physical methods ($n=4$) and sympathectomy ($n=3$).	Heterogeneous responses with symptom improvement reported in 40% of individuals treated with antidepressants, 21% with aspirin, 7% with nonsteroidal anti-inflammatory drugs, 30% with topical lidocaine, 7% with systemic corticosteroids, 50% with physical methods and 33% with sympathectomy, whereas no improvement was reported with antihistamines.
Poterucha et al. (2013)	United States	Retrospective case series	Paediatric and adult individuals with erythromelalgia treated with topical amitriptyline–ketamine. Small-fibre neuropathy, based on characteristic autonomic symptoms or autonomic testing, was identified in 24 individuals (67%). Large-fibre neuropathy was additionally reported in 3 individuals (8%) and motor neuropathy in 2 (6%).	Aetiological subtype not clearly stratified ($n=36$)	44 [5–74]	To evaluate the effect of topical amitriptyline– ketamine in erythromelalgia.	Daily topical gel/cream: –1% amitriptyline +0.5% ketamine ($n=29$) –2% amitriptyline +0.5% ketamine ($n=4$) –2% amitriptyline +0.5% ketamine +2% lidocaine ($n=3$).	Topical amitriptyline–ketamine (with or without lidocaine) was associated with a clinical improvement in 75% of treated individuals, including complete relief in 3%, significant relief in 39% and partial relief in 33%. The presence of small-fibre neuropathy was not significantly associated with treatment response ($p=0.69$).

(Continues)

TABLE 2 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[a]	Age[b]	Main study focus	Treatment strategies	Effect on erythromelalgia
Huang et al. (2014)	China	Prospective observational cohort study with a comparison group	Adult individuals with advanced myeloproliferative neoplasms, including essential thrombocythaemia in 123 individuals (47.5%) and polycythaemia vera in 136 (52.5%). JAK2V617F status was documented in the entire cohort: 202 individuals (78.0%) were positive and 57 (22.0%) were negative. Erythromelalgia was assessed as a secondary vasomotor outcome.	Secondary ($n = 29$)	47 [26–65]	To evaluate the effect of interferon-α-2b on symptoms in essential thrombocythaemia and polycythaemia vera, including erythromelalgia.	IFN-α-2b: 9 million units SC/week for 2 years, then 10 million units SC weekly; control: hydroxyurea (standard first-line therapy).	Interferon-α-2b was associated with lower erythromelalgia rates at follow-up than hydroxyurea in polycythaemia vera (9.4% vs. 29.2%; $p < 0.01$). No comparative analysis was available for essential thrombocythaemia because of the limited number of cases.
Pagani-Estévez et al. (2017)	United States	Retrospective case series	Individuals with erythromelalgia treated with corticosteroids. An autoimmune or inflammatory background was reported in 17 individuals (55%). Small-fibre neuropathy was supported by abnormal autonomic reflex screening in 15 of the 22 individuals assessed (68%) and abnormal thermoregulatory sweat testing in 18 of 24 (75%). Large-fibre neuropathy was identified in 6 of 22 individuals (27%), vascular abnormalities in 13 of 22 (59%) and myeloproliferative neoplasms in 3 individuals (10%).	Aetiological subtype not clearly stratified ($n = 31$)	47 (26–57)	To identify clinical predictors of corticosteroid responsiveness in erythromelalgia.	Systemic corticosteroid therapy (individualised dosing, including high-dose corticosteroid protocols).	Corticosteroid treatment was associated with a clinical response in 17 of 31 individuals (55%), including 8 partial and 9 complete responses. Responders received corticosteroids earlier and more frequently had a subacute disease course reaching peak severity within 21 days. An infectious, traumatic, or surgical precipitant was particularly associated with complete response.

(Continues)

TABLE 2 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[a]	Age[b]	Main study focus	Treatment strategies	Effect on erythromelalgia
Akabane et al. (2022)	United States	Retrospective case series	Individuals with erythromelalgia and biopsy-confirmed reduced epidermal nerve density, consistent with small-fibre loss. Reported aetiologies included autoimmune conditions in 12 individuals (46.2%), idiopathic forms in 5 (19.2%) and genetic or hereditary forms in 3 (11.5%). An *SCN9A* variant was identified in 2 individuals (7.7%), although the total number undergoing genetic testing was not reported.	Aetiological subtype not clearly stratified ($n = 26$)	46.5 [NR]	To evaluate treatment response in erythromelalgia associated with biopsy-proven small-fibre loss.	Heterogeneous treatments, mainly intravenous immunoglobulin ($n = 11$), tricyclic antidepressants ($n = 10$), systemic corticosteroids ($n = 9$), selective serotonin reuptake inhibitors ($n = 9$), gabapentin ($n = 9$) and mexiletine ($n = 4$).	Heterogeneous responses were reported, with symptom improvement in 66.7% of individuals treated with systemic corticosteroids, 63.7% with intravenous immunoglobulin, 55.6% with selective serotonin reuptake inhibitors, 50.0% with tricyclic antidepressants and 44.4% with gabapentin. Mexiletine was associated with improvement in 3 of 4 individuals (75.0%), including both individuals with an identified *SCN9A* variant.
Michelerio et al. (2023)	Italy	Retrospective case series	Female individuals with primary erythromelalgia. *SCN9A* sequencing was performed in all individuals: four carried heterozygous variants, although a pathogenic variant was identified in only one. Two individuals with negative genetic testing had a suggestive family history. Neurophysiological testing was performed in all individuals and identified small-fibre neuropathy in 3 (27%). Skin biopsies performed in 3 individuals showed vascular abnormalities.	Primary ($n = 11$)	36 [16–57]	To characterise the clinical, genetic, neurophysiological and therapeutic features of primary erythromelalgia.	Heterogeneous; mainly antihistamines ($n = 10$), mexiletine ($n = 5$), magnesium supplementation ($n = 5$), venlafaxine ($n = 5$), aspirin ($n = 5$).	Heterogeneous responses were observed, with symptom improvement in 80% of individuals treated with mexiletine, 60% with magnesium supplementation, 40% with antihistamines, 20% with venlafaxine and 0% with aspirin.

(Continues)

TABLE 2 | (Continued)

First author (year)	Country	Study design	Population	Type of erythromelalgia[a]	Age[b]	Main study focus	Treatment strategies	Effect on erythromelalgia
Sun et al. (2023)	United States	Retrospective case series	Paediatric individuals with erythromelalgia. Three individuals (7%) had a confirmed pathogenic *SCN9A* variant, while 6 (14%) had novel candidate variants under investigation. Skin biopsy was performed in 4 individuals (10%) and was consistent with small-fibre neuropathy in 3 of those assessed (75%; 7% of the overall cohort). Electromyography and nerve conduction studies were performed in 10 individuals (24%) and were abnormal in 2 (20%; 5% of the overall cohort).	Primary ($n=41$); Secondary ($n=1$)	13 [7–15]*	To characterise paediatric erythromelalgia, with emphasis on clinical features and treatment response.	Heterogeneous; including gabapentin ($n=22$), aspirin ($n=15$), topical lidocaine ($n=14$), mexiletine ($n=10$), intravenous lidocaine ($n=10$), corticosteroids ($n=5$).	Heterogeneous responses were reported across treatments, with clinical improvement observed in 60% of individuals receiving intravenous lidocaine, 45% with gabapentin, 40% with mexiletine, 30% with topical lidocaine, 25% with aspirin and 20% with corticosteroids.
Ducrocq et al. (2025)	France	Retrospective case series, with functional assays	Paediatric and adult individuals with refractory primary erythromelalgia and persistent pain rated ≥4/10 despite conventional analgesics or intolerance to previous treatments. Whole-exome sequencing identified pathogenic *SCN9A* variants in 3 individuals (42.9%); the remaining 4 individuals (57.1%) had idiopathic primary erythromelalgia.	Primary ($n=7$)	16 [4–45]	To assess the efficacy and safety of topical mepyramine in primary erythromelalgia.	Topical 20% mepyramine compounded cream applied to painful areas during attacks for 3 months.	Topical mepyramine was associated with rapid reduction of pain and erythema within 5–10 min in all treated individuals, with responses ranging from moderate to marked relief. Pain intensity decreased by 44%–88%, accompanied by reductions in attack frequency and duration in most individuals. Functional analyses demonstrated inhibition of mutant $Na_v1.7$ channels and normalisation of pathological channel gating, supporting reversal of neuronal hyperexcitability.

[a]Type of erythromelalgia was reported as defined in the original publication or based on information provided by the authors.
[b]Age is reported as median [range]; when unavailable, median (Q1–Q3) is indicated by an asterisk (*). 'NR' indicates that data were not reported.

both comparisons). Concomitant cytoreductive therapies were similarly distributed between the two dosing groups, thereby limiting potential confounding by disease-directed treatment (Rocca et al. 2024).

Among individuals with myeloproliferative neoplasms, therapies directed at the underlying disease were also associated with improvement in erythromelalgia. In one prospective study, anagrelide was associated with complete symptom resolution following achievement of a sustained platelet response in essential thrombocythaemia-associated erythromelalgia (Cacciola et al. 2005). In a prospective comparative study involving individuals with essential thrombocythaemia or polycythaemia vera, erythromelalgia was less frequent with interferon-α-2b than with hydroxyurea (9.4% vs. 29.2%; $p < 0.01$) (Huang et al. 2014).

3.4.2 | Topical Treatments

Topical therapies showed heterogeneous efficacy. In a cohort not stratified by aetiological subtype, topical amitriptyline–ketamine was associated with clinical improvement in 75% of treated individuals. Treatment response was not significantly associated with the presence of small-fibre neuropathy ($p = 0.69$) or with hand or facial involvement ($p = 0.33$) (Poterucha et al. 2013).

By contrast, in a small randomised, placebo-controlled crossover study in which participants were not stratified according to erythromelalgia subtype, topical amitriptyline monotherapy did not demonstrate superiority over placebo. Mean pain-attack intensity scores were similar during amitriptyline and placebo treatment (4.47 ± 1.68 vs. 4.50 ± 1.69, respectively), with no statistically significant difference ($p = 0.09$) (AlgoTherapeutix 2025).

Among studies restricted to primary erythromelalgia, a small case series reported reductions in pain intensity of 44%–88% with topical mepyramine (Ducrocq et al. 2025). Topical XPF-002 was also associated with lower cooling requirements than placebo; however, interpretation was substantially limited by the marked difference in group sizes, as seven individuals received XPF-002 and only one received placebo (Xenon Pharmaceuticals 2014).

3.4.3 | Interventional Approaches

Sympathetic interventions were evaluated in small and heterogeneous populations. The most detailed evidence came from an uncontrolled prospective study of chemical lumbar sympathectomy in 13 individuals with refractory erythromelalgia, including 10 with primary and 3 with secondary forms. Mean pain intensity decreased from 8.2 ± 2.0 at baseline to 4.9 ± 2.7 after 1 day and 1.9 ± 3.0 after 1 week. A complete response was achieved in 69.2% (9/13) of individuals, with sustained benefit at 2 years in 55.6% (5/9) of initial responders (Wang et al. 2018). Retrospective case series reporting outcomes following sympathectomy and other sympathetic procedures, without aetiological stratification, described more variable results, with partial benefit reported in 33%–50% of individuals (Davis et al. 2000; Cook-Norris et al. 2012).

3.4.4 | Non-Pharmacological

Non-pharmacological strategies were infrequently evaluated. Physical methods were reported within heterogeneous retrospective case series, with limited and inconsistently defined treatment-response data (Davis et al. 2000; Cook-Norris et al. 2012). In a small retrospective cohort without aetiological or pathophysiological characterisation, an intensive multidisciplinary pain rehabilitation programme was associated with significant improvements in pain-related interference (52.5 ± 8.7 to 39.7 ± 11.7; $p = 0.045$), life control (49.1 ± 7.8 to 57.3 ± 4.3; $p = 0.046$) and general activity (46.6 ± 4.2 to 54.0 ± 7.4; $p = 0.047$) (Durosaro et al. 2008).

The main findings regarding pain management strategies are summarised in Tables 1 and 2 for interventional and observational studies, respectively.

3.5 | Secondary Outcomes

3.5.1 | Adverse Events and Treatment Tolerability

Adverse events were inconsistently reported across studies and were generally mild when documented. Prostaglandin analogues were primarily associated with transient headache, flushing and gastrointestinal symptoms, which were self-limiting or resolved after treatment discontinuation (Kalgaard et al. 2003; Mørk et al. 2004). Oral sodium-channel blockers were associated with dose-dependent neurological and gastrointestinal adverse effects, although no major safety concerns were identified in the included studies (Fischer et al. 2009; Geha et al. 2016; Wang et al. 2022). Safety data for oral selective $Na_v1.7$ inhibitors remained limited. Early-phase trials did not identify major safety concerns, but treatment exposure was short, precluding conclusions regarding long-term safety and tolerability (Goldberg et al. 2012; Cao et al. 2016; Pfizer 2019).

Topical therapies were generally well tolerated. Amitriptyline, amitriptyline–ketamine combinations, mepyramine and lidocaine-based formulations were associated mainly with local or mild adverse events, with no consistent systemic safety signal reported (Poterucha et al. 2013; AlgoTherapeutix 2025; Ducrocq et al. 2025). Topical XPF-002 was evaluated in a single early-phase study, and the available safety data were limited (Xenon Pharmaceuticals 2014).

Chemical lumbar sympathectomy was associated with transient localised post-procedural pain, with no other major adverse events reported. However, conclusions regarding its safety remain limited because the evidence was derived from a single prospective study involving a small number of individuals (Wang et al. 2018).

3.5.2 | Health-Related Quality of Life and Functional Outcomes

Health-related quality-of-life and functional outcomes were rarely assessed across the included studies. Significant

functional improvements were reported only in the study evaluating a multidisciplinary rehabilitation programme, limiting conclusions regarding the broader effects of the interventions on daily functioning and quality of life (Durosaro et al. 2008).

3.5.3 | Mechanistic and Aetiological Data

Aetiological subtype was reported for 277 of 591 individuals (46.9%). Reporting was more complete among interventional studies, with 11 of 12 studies specifying whether erythromelalgia was primary or secondary, compared with 7 of 13 observational studies. However, this classification did not necessarily include direct characterisation of the underlying mechanism.

Beyond subtype classification, more detailed mechanistic and aetiological characterisation varied across domains. Haematological data concerning myeloproliferative neoplasms were available for 429 of 591 individuals (72.6% of the total study population), *SCN9A* status for 112 (19.0%), data on large-fibre or axonal neuropathy for 99 (16.8%), data on small-fibre neuropathy for 94 (15.9%), data on an autoimmune or inflammatory background for 78 (13.2%) and functional vascular data for 52 (8.8%).

Among those assessed in each domain, a myeloproliferative neoplasm was documented in 157 of 429 individuals (36.6%), a pathogenic or disease-associated variant in *SCN9A* in 45 of 112 (40.2%), large-fibre or axonal neuropathy in 29 of 99 (29.3%), small-fibre neuropathy or biopsy-confirmed small-fibre loss in 66 of 94 (70.2%), an autoimmune or inflammatory background in 32 of 78 (41.0%) and functional vascular abnormalities in 31 of 52 (59.6%). These domains were not mutually exclusive, and the varying denominators reflect the non-systematic assessment and reporting of mechanistic and aetiological features across studies.

The clearest aetiology-specific treatment-response pattern concerned erythromelalgia associated with myeloproliferative neoplasms. In this setting, findings across studies supported a beneficial effect of aspirin, whereas studies of primary or aetiologically unstratified erythromelalgia provided very limited evidence of benefit (Davis et al. 2000; Michiels et al. 2003, 2006; Cook-Norris et al. 2012; Michelerio et al. 2023; Rocca et al. 2024). Improvement was also reported following treatment with anagrelide and achievement of platelet reduction, suggesting that control of the underlying myeloproliferative disorder may contribute to symptom resolution (Cacciola et al. 2005).

Among individuals carrying pathogenic *SCN9A* variants, responses to sodium-channel–targeted therapies were frequently reported, suggesting a potential relationship between the underlying channel dysfunction and treatment response (Goldberg et al. 2012; Cao et al. 2016; Geha et al. 2016; Akabane et al. 2022; Wang et al. 2022). However, these findings were based on only a small number of individuals, precluding firm conclusions regarding treatment efficacy in this subgroup. In other forms of erythromelalgia, the available data were derived mainly from mixed cohorts in which treatment outcomes were not reported separately by aetiological subtype, preventing assessment of effectiveness within individual subgroups.

Beyond pharmacological treatment, relapse following chemical lumbar sympathectomy appeared to be more frequent among individuals with *SCN9A*-associated erythromelalgia, raising the possibility that *SCN9A* status may also influence the durability of response to sympathetic interventions. However, this observation was based on a very small number of individuals (Wang et al. 2018).

Overall, the available findings point to potential associations between underlying mechanisms and treatment response, but the evidence remains insufficient to support clinical recommendations for mechanism-based treatment selection. Detailed summaries of adverse events and variant-level data are provided in Appendices S3 and S4, respectively.

3.6 | Certainty of Evidence

According to the GRADE framework (Guyatt et al. 2011; Balshem et al. 2011), evidence for aspirin in myeloproliferative neoplasm-associated erythromelalgia was initially rated as low certainty because it was derived predominantly from observational studies and remained susceptible to confounding. It was upgraded by one level to moderate certainty because the reported treatment–response signal was large and generally consistent within this clearly defined subgroup, with rapid symptom relief, recurrence after aspirin withdrawal and fewer pain episodes with twice-daily than once-daily dosing, while concomitant cytoreductive therapies were similarly distributed between groups.

By contrast, evidence for both anagrelide and interferon-α-2b in myeloproliferative neoplasm-associated erythromelalgia was rated as very low certainty. For anagrelide, the evidence came from a single small prospective uncontrolled study and was downgraded for serious imprecision. For interferon-α-2b, the rating reflected the non-randomised design, the assessment of erythromelalgia as a secondary outcome, and the inability to distinguish a specific effect of interferon-α-2b on erythromelalgia from the effect of treating the underlying neoplasm.

In primary erythromelalgia, evidence for the conventional sodium-channel blockers mexiletine and carbamazepine was rated as low certainty. Although favourable treatment responses were reported across several studies, no upgrading was applied because the evidence was based on very small samples.

Across different aetiological populations, evidence for prostaglandin analogues was rated as low certainty. Although controlled data were available, certainty was downgraded because the evidence was limited to two small studies with inconsistent comparative findings. Misoprostol improved pain and cooling-related outcomes compared with placebo in a fixed-sequence crossover study, whereas iloprost showed significant within-group improvements but no statistically significant between-group differences. These findings suggest a possible therapeutic signal but are insufficient to establish a consistent treatment effect.

Evidence for corticosteroids and sympathetic interventions was rated as low certainty because it was derived mainly from small, uncontrolled or non-randomised studies. Evidence for

selective $Na_v1.7$ inhibitors was rated as very low certainty owing to extremely small samples, short treatment exposure, variable results and the frequent use of experimentally induced heat-evoked pain rather than spontaneous pain outcomes.

For topical preparations, evidence for amitriptyline–ketamine was rated as low certainty because it was derived from an uncontrolled study. Evidence for mepyramine and XPF-002 was rated as very low certainty because of the very small samples, with additional concern regarding the marked treatment-group imbalance in the XPF-002 study. Evidence for topical amitriptyline monotherapy was rated as low certainty and remained inconclusive: a single crossover trial involving 13 individuals did not demonstrate superiority over placebo, but the imprecision associated with the small sample was insufficient to exclude a clinically meaningful benefit.

Evidence for non-pharmacological interventions and other oral therapies, including gabapentin, antidepressants, antihistamines and magnesium, was rated as very low certainty because the available data were limited, heterogeneous and largely derived from retrospective studies with predominantly qualitative and non-comparative outcome reporting.

A more detailed domain-level justification for each certainty rating is provided in Table 3.

4 | Discussion

This systematic review provides a structured and graded appraisal of pain-management strategies in erythromelalgia. Moderate-certainty evidence was limited to aspirin in myeloproliferative neoplasm-associated erythromelalgia. Low-certainty evidence suggested potential benefit from the conventional sodium-channel blockers mexiletine and carbamazepine in primary erythromelalgia, as well as from prostaglandin analogues, corticosteroids, selected topical therapies and sympathetic interventions in specific clinical contexts. Evidence for selective $Na_v1.7$ inhibitors and most other interventions was of very low certainty. Topical amitriptyline monotherapy did not demonstrate superiority over placebo in a single small crossover trial; however, the evidence remained inconclusive because the small sample was insufficient to exclude a clinically meaningful effect. Findings supported by very low-certainty evidence should be regarded as hypothesis-generating and require further confirmation before they can support treatment-specific recommendations for erythromelalgia. Findings supported by low-certainty evidence should also be interpreted cautiously, as the true effect may differ substantially from the estimated effect.

Data on erythromelalgia subtype and underlying mechanisms were examined as secondary outcomes. Classification as primary or secondary erythromelalgia was reported for 46.9% of individuals. The availability of more detailed aetiological and mechanistic data varied according to the domain assessed. Haematological or relevant biological data concerning myeloproliferative neoplasms were available for 72.6% of the total study population, *SCN9A* status for 19.0%, and data on small-fibre neuropathy for 15.9%. This incomplete and heterogeneous reporting limited the assessment of potential associations between underlying mechanisms and treatment response, particularly within primary erythromelalgia, which encompasses both genetic and idiopathic forms (Caldito et al. 2024).

In *SCN9A*-associated forms, favourable responses to conventional sodium-channel blockers have been reported, suggesting a potentially relevant therapeutic signal. Although the small sample sizes preclude firm conclusions, the observed responses are consistent with the underlying mechanism, as gain-of-function alterations of $Na_v1.7$ increase nociceptor excitability (Dib-Hajj et al. 2005, 2013). This clinical and functional concordance was illustrated in a family carrying the *SCN9A* p.Val-400Met variant, in which carbamazepine produced substantial clinical improvement in affected members and normalised the altered gating of mutant $Na_v1.7$ (Fischer et al. 2009). Preliminary findings suggest that this mechanistic rationale may also extend to topical sodium-channel modulation. In a small case series of primary erythromelalgia, mepyramine, shown in functional experiments to inhibit mutant $Na_v1.7$ channels, was associated with reductions in pain intensity of 44%–88%; however, the very small uncontrolled design substantially limits confidence in the observed treatment effect (Hao et al. 2021; Ducrocq et al. 2025).

Beyond genetic status, peripheral nerve involvement may represent another relevant factor when interpreting treatment responses in primary erythromelalgia. Among those assessed, small-fibre neuropathy or biopsy-confirmed small-fibre loss was frequently documented, including in both idiopathic and *SCN9A*-associated forms, suggesting that neuropathic involvement may occur across aetiological categories (Caldito et al. 2024; Akabane et al. 2022). However, because treatment outcomes were rarely stratified according to neuropathy status, it remains unclear whether such involvement predicts response to conventional sodium-channel blockers or to treatments recommended for neuropathic pain, including gabapentinoids and antidepressants (Soliman et al. 2025). Gabapentinoids and antidepressants were sparsely evaluated in erythromelalgia, and the available evidence was non-comparative (Cook-Norris et al. 2012; Akabane et al. 2022).

Microvascular and sympathetic pathways may represent additional therapeutic targets in erythromelalgia, but the supporting evidence was sparse and inconsistent. Among prostaglandin analogues, misoprostol improved pain and cooling-related outcomes compared with placebo, whereas iloprost produced within-group improvements without statistically significant between-group differences (Kalgaard et al. 2003; Mørk et al. 2004). Pain reductions following chemical lumbar sympathectomy in refractory erythromelalgia further suggest potential therapeutic benefit from sympathetic modulation (Davis et al. 2000; Cook-Norris et al. 2012; Wang et al. 2018). However, evidence for sympathetic interventions was limited to very small uncontrolled studies and should be regarded as exploratory rather than as establishing their efficacy or safety.

Among secondary forms, the strongest treatment evidence concerned aspirin in myeloproliferative neoplasm-associated erythromelalgia. Across studies, aspirin was associated with rapid and generally consistent symptom relief, recurrence after treatment withdrawal, and fewer pain episodes with twice-daily than once-daily dosing (Michiels et al. 2003, 2006; Rocca et al. 2024).

TABLE 3 | GRADE assessment of therapeutic strategies in erythromelalgia.

Therapeutic strategy[a]	Key studies	Certainty of evidence (GRADE)[b]	Rationale for rating
Aspirin	Michiels et al. (2003); Michiels et al. (2006); Rocca et al. (2024)	Moderate—myeloproliferative neoplasm-associated erythromelalgia	Evidence was derived predominantly from observational studies and therefore remained susceptible to confounding. Rocca et al. (2024) provided supportive but indirect evidence because erythromelalgia was a secondary endpoint in a trial primarily comparing once- versus twice-daily low-dose aspirin in individuals with myeloproliferative neoplasms. Nevertheless, the overall treatment-response signal was large and generally consistent within this clearly defined subgroup, including rapid symptom relief, recurrence after aspirin withdrawal and fewer pain episodes with twice-daily than once-daily dosing. In the comparative study, concomitant cytoreductive therapies were similarly distributed between groups, limiting confounding by disease-directed treatment. The evidence was therefore upgraded by one level from low to moderate certainty.
Conventional sodium-channel blockers (mexiletine, carbamazepine)	Davis et al. (2000); Fischer et al. (2009); Geha et al. (2016); Wang et al. (2022); Akabane et al. (2022); Michelerio et al. (2023); Sun et al. (2023)	Low—primary erythromelalgia	Evidence comprised one very small controlled trial, one prospective single-arm interventional study and several observational case series. Although favourable responses to mexiletine and carbamazepine were reported across studies, the controlled evidence involved an extremely small sample, genotype-stratified findings were limited to very small subgroups, and treatment-specific attribution was not always possible in sequential or multimodal regimens. Overall certainty was rated as low because of serious imprecision and the predominance of uncontrolled evidence, and no upgrading was applied.
Prostaglandin analogues (iloprost, misoprostol)	Kalgaard et al. (2003); Mørk et al. (2004)	Low—across different aetiological populations	Evidence was derived from one small placebo-controlled randomised pilot trial and one placebo-controlled, non-randomised fixed-sequence crossover study. Misoprostol improved pain and cooling-related outcomes compared with placebo, whereas iloprost produced significant within-group improvements but no statistically significant between-group differences. Certainty was downgraded because of risk of bias, inconsistency and imprecision.
Systemic corticosteroids	Davis et al. (2000); Cook-Norris et al. (2012); Pagani-Estévez et al. (2017); Akabane et al. (2022); Sun et al. (2023)	Low—heterogeneous or non-stratified populations	Evidence was derived predominantly from retrospective case series. Although marked improvement was reported in a possible corticosteroid-responsive subset, responses varied substantially across studies. Interpretation was limited by heterogeneous regimens, inconsistent etiological characterisation, retrospective outcome assessment and the absence of controlled comparisons.

(Continues)

TABLE 3 | (Continued)

Therapeutic strategy[a]	Key studies	Certainty of evidence (GRADE)[b]	Rationale for rating
Sympathetic interventions, including chemical and surgical sympathectomy	Davis et al. (2000); Cook-Norris et al. (2012); Wang et al. (2018)	Low—refractory erythromelalgia	Evidence was derived from one small prospective uncontrolled study and two retrospective case series evaluating heterogeneous sympathetic procedures. Although reductions in pain intensity and sustained improvement were reported following chemical lumbar sympathectomy, outcomes with other sympathetic interventions were more variable. Uncontrolled designs, small sample sizes, heterogeneous populations and techniques, limited adverse-event reporting, and the absence of independent prospective replication precluded firm conclusions regarding either efficacy or safety. Overall, the certainty of evidence was rated as low.
Topical amitriptyline monotherapy	AlgoTherapeutix (2025)	Low and inconclusive—etiological subtype not stratified	Evidence was derived from a single small randomised placebo-controlled crossover trial reported only in a trial registry. The study did not demonstrate superiority over placebo, but the sample of 13 individuals and limited reporting produced serious imprecision and were insufficient to exclude a clinically meaningful benefit.
Topical amitriptyline–ketamine	Poterucha et al. (2013)	Low—etiological subtype not stratified	Evidence was derived from a relatively large single-centre retrospective case series for this rare condition. Pain relief was assessed through medical-record review using predefined categories ranging from complete relief to worsening, and small-fibre neuropathy status was also evaluated. Despite the comparatively large sample size and structured response assessment, certainty remained limited by the absence of a comparator, retrospective outcome ascertainment and lack of independent replication.
Anagrelide	Cacciola et al. (2005)	Very low[c]—essential thrombocythaemia-associated erythromelalgia	Evidence was limited to a single small prospective uncontrolled study. Complete symptom resolution was reported following achievement of a sustained platelet response, but the absence of a comparator, serious imprecision and the inability to distinguish a specific effect of anagrelide on erythromelalgia from the effect of controlling the underlying neoplasm substantially limited certainty.
Topical mepyramine and topical XPF-002	Xenon Pharmaceuticals (2014); Ducrocq et al. (2025)	Very low[c]—primary erythromelalgia	Evidence was limited to two very small studies. Mepyramine was evaluated in a small case series, while XPF-002 was reported only in a trial registry and involved marked treatment-group imbalance, with seven individuals receiving active treatment and one receiving placebo. Certainty was downgraded because of serious risk of bias and very serious imprecision.

(Continues)

TABLE 3 | (Continued)

Therapeutic strategy[a]	Key studies	Certainty of evidence (GRADE)[b]	Rationale for rating
Oral selective $Na_v1.7$ inhibitors (PF-05089771, XPF-002)	Goldberg et al. (2012); Cao et al. (2016); Pfizer (2019)	Very low[c]—primary erythromelalgia	Evidence was derived from three extremely small placebo-controlled early-phase trials. Findings were variable, one study did not meet its primary endpoint, and efficacy was frequently assessed using experimentally induced heat-evoked pain rather than spontaneous erythromelalgia symptoms. Short treatment exposure, serious imprecision, indirectness, inconsistency and registry-only reporting for one study further reduced certainty.
Interferon-α-2b	Huang et al. (2014)	Very low[c]—myeloproliferative neoplasm-associated erythromelalgia	Evidence was derived from a single non-randomised prospective comparison in which erythromelalgia was assessed as a secondary outcome. Erythromelalgia was less frequent with interferon-α-2b than with hydroxyurea, but the specific effect of interferon-α-2b on erythromelalgia could not be distinguished from the effect of treating the underlying neoplasm. Certainty was rated as very low because of the non-randomised design, secondary-outcome assessment, small sample size and absence of independent replication.
Other oral therapies, including gabapentin, antidepressants, antihistamines and magnesium	Davis et al. (2000); Cook-Norris et al. (2012); Akabane et al. (2022); Michelerio et al. (2023); Sun et al. (2023)	Very low[c]—heterogeneous or non-stratified populations	Evidence was derived largely from retrospective case series evaluating heterogeneous therapies, frequently within multimodal or sequential regimens. Reported responses varied substantially, and treatment-specific effects could rarely be determined. Certainty was limited by uncontrolled designs, small samples, heterogeneous outcome definitions and predominantly qualitative reporting.
Non-pharmacological interventions, including physical methods, TENS and multidisciplinary pain rehabilitation	Davis et al. (2000); Durosaro et al. (2008); Cook-Norris et al. (2012)	Very low[c]—etiological subtype not stratified	Evidence was derived exclusively from small observational studies. Although improvements in symptom burden, functioning or pain-related interference were reported, interventions and outcomes were heterogeneous and no controlled confirmatory data were available. Certainty was downgraded because of serious risk of bias, imprecision, indirectness and lack of replication.

[a]Therapeutic strategies specified in parentheses refer to the specific drugs or interventions within a broader therapeutic category to which the reported level of evidence applies.
[b]Certainty was assessed using the standard GRADE domains of risk of bias, inconsistency, indirectness, imprecision and publication bias. The clinical context stated after each certainty rating indicates the population to which that rating applies. Registry-only reporting and uncertainty regarding the completeness of outcome reporting were considered in the relevant domains.
[c]Findings supported by very low-certainty evidence should be regarded as hypothesis-generating and are insufficient to support treatment-specific recommendations for erythromelalgia.

These findings support a treatment effect in this specific subgroup and are consistent with the proposed involvement of platelet-mediated microvascular dysfunction (Van Genderen and Michiels 1997; Michiels 2002).

Evidence for treatments targeting inflammatory or immune pathways was much more limited. In one retrospective series, corticosteroid responsiveness was observed in a subset of individuals, particularly among those with a subacute disease course (Pagani-Estévez et al. 2017). Responses varied across other retrospective series, and corticosteroids were not evaluated in clearly defined inflammatory subgroups (Cook-Norris et al. 2012; Akabane et al. 2022). Other immunomodulatory approaches were only sporadically reported, with insufficient treatment-specific data to draw firm conclusions (Davis et al. 2000; Akabane et al. 2022). These observations suggest that inflammatory or immune-mediated mechanisms may contribute to selected presentations, but the evidence remains too limited and heterogeneous to establish a distinct pathophysiological subtype or inform treatment selection (Caldito et al. 2024).

Taken together, these findings suggest that treatment response in erythromelalgia may depend, at least in part, on the underlying biological pathway, and that improved mechanistic characterisation could help guide treatment selection. However, the available evidence remains insufficient to support such a mechanism-informed approach in clinical practice.

Methodologically, this review applied predefined eligibility criteria, independent study selection and data extraction, structured risk-of-bias assessment and GRADE evaluation. The prespecified five-participant threshold for non-randomised studies was intended to limit reliance on isolated reports and very small uncontrolled series, in which apparent treatment effects are difficult to distinguish from spontaneous symptom fluctuations or between-individual variability. This threshold determined eligibility rather than methodological quality. RCTs involving fewer than five participants were retained because random allocation and a within-study comparator provided a basis for direct within-study comparison, but their substantial imprecision was reflected in the GRADE assessment and the findings were interpreted as exploratory.

In line with methodological guidance for rare diseases, the rarity of erythromelalgia was considered when contextualising the availability of evidence and the feasibility of different study designs, while standard GRADE criteria were applied without modification (Pai et al. 2015, 2019). Certainty ratings therefore reflected the limitations of the evidence itself, particularly uncontrolled designs, incomplete outcome reporting, small sample sizes, limited numbers of events and heterogeneity in interventions and outcome assessment (Balshem et al. 2011; Guyatt et al. 2011). A quantitative meta-analysis was not performed because of substantial clinical and methodological heterogeneity across studies, interventions and outcome definitions, making a narrative synthesis more appropriate.

Several limitations should be acknowledged. First, the evidence base was limited in size and methodological quality. Although the 25 included studies collectively reported 591 individuals, almost half were retrospective case series, and most interventions were evaluated in small populations. Uncontrolled designs, retrospective outcome ascertainment, heterogeneous treatment exposures and inconsistent outcome definitions frequently limited causal attribution and resulted in substantial imprecision. The small number of studies available for each intervention also precluded a reliable formal assessment of publication bias.

Second, characterisation of erythromelalgia subtype, underlying mechanisms and pain phenotype was incomplete, particularly in retrospective studies. Classification as primary or secondary erythromelalgia did not necessarily establish the underlying mechanism, while genetic, physiological, biomarker, sensory and neuropathy data were inconsistently reported. The presence of an associated condition alone was not considered sufficient to establish secondary erythromelalgia or causality. Consequently, analyses of potential associations between mechanisms, pain presentation and treatment response relied partly on biological plausibility and cross-study interpretation rather than direct comparative evidence.

Third, follow-up was often short, and adverse events, long-term safety, physical functioning, quality of life, treatment acceptability and patient global assessment were inconsistently reported. In addition, three included reports were available only as ClinicalTrials.gov results records without corresponding peer-reviewed publications (Xenon Pharmaceuticals 2014; Pfizer 2019; AlgoTherapeutix 2025). The limited methodological and analytical detail available for these records complicated risk-of-bias assessment and created uncertainty regarding the completeness of outcome reporting.

Finally, excluding non-randomised studies involving fewer than five participants reduced reliance on isolated uncontrolled observations but also narrowed the range of therapeutic approaches represented in the review. Several interventions reported only in isolated case reports or very small case series were therefore not eligible for inclusion. This was particularly relevant to neuromodulation strategies, including spinal cord stimulation, dorsal root ganglion stimulation and repetitive transcranial magnetic stimulation, for which the available publications did not meet the prespecified eligibility criteria (Hagedorn et al. 2021; Lee et al. 2024). Their absence from the evidence synthesis should not be interpreted as evidence of ineffectiveness, but rather as indicating a lack of eligible evidence. A registered randomised, sham-controlled crossover trial is evaluating burst spinal cord stimulation in refractory erythromelalgia (St. Olavs Hospital 2019), illustrating emerging efforts to evaluate neuromodulation using more rigorous study designs.

Future research should prioritise international, multicentre prospective studies using standardised diagnostic criteria and systematic classification of erythromelalgia subtype. An international multidisciplinary consensus involving clinicians and researchers could help harmonise diagnostic criteria, subtype classification and treatment pathways. Individuals should be stratified according to primary or secondary erythromelalgia and, whenever possible, according to specific genetic, haematological, inflammatory, vascular or neurological characteristics. Genotype-stratified studies are particularly needed to determine whether pathogenic variants in *SCN9A* or other sodium-channel genes predict response to sodium-channel-targeted

therapies. More broadly, prospective studies should test whether treatment selection based on systematic subtype and mechanistic characterisation improves clinical outcomes compared with non-stratified approaches.

Given the rarity and clinical variability of erythromelalgia, conventional parallel-group randomised trials may not always be feasible. Randomised crossover trials may offer an efficient approach to comparing treatments within individuals, while international registries could provide larger longitudinal datasets on treatment effectiveness, safety and therapeutic trajectories. Future studies should consistently assess pain intensity, attack frequency and duration, cooling requirements, physical functioning, adverse events, treatment discontinuation and patient-reported outcomes, with sufficiently long follow-up to evaluate the durability of benefit and long-term safety.

Overall, moderate-certainty evidence was confined to aspirin in myeloproliferative neoplasm-associated erythromelalgia, while most other interventions were supported by low- or very low-certainty evidence. Findings from better-characterised populations suggest that underlying mechanisms may influence treatment response, but prospective studies with systematic subtype and mechanistic characterisation are needed before mechanism-informed treatment selection can be recommended in clinical practice.

Author Contributions

C.R. contributed to study design, protocol registration, literature search, study screening, data extraction, certainty of evidence assessment and drafted the manuscript. S.B. contributed to study design, literature search, study screening and data extraction. J.F. contributed to the literature search, certainty of evidence assessment and drafted part of the Supporting Information. M.L. contributed to data extraction and risk-of-bias assessment. A.D.P. contributed to the interpretation of pharmacological data and drafted part of the Supporting Information. I.D. contributed to risk-of-bias assessment. L.E. contributed to the literature search and identification of relevant studies. X.M. and E.S. contributed to study design and critically reviewed the manuscript for important intellectual content. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Acknowledgements

Open access publication funding provided by COUPERIN CY26.

Funding

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data analysed in this study were derived from published articles. The data extraction forms and extracted datasets are available from the corresponding author upon reasonable request.

References

Akabane, H., C. Ikenaga, Y. Saito, M. Nakagawa, and T. Yamaguchi. 2022. "Clinical Characteristics and Treatment Responses in Erythromelalgia: A Retrospective Observational Study." *Journal of Dermatology* 49: 1010–1017. https://doi.org/10.1111/1346-8138.16412.

Algarni, A. S., R. M. Alharthi, S. O. Alqurashi, et al. 2025. "Comparative Efficacy and Tolerability of Treatments for Erythromelalgia: A Systematic Review." *Medicina* 61, no. 5: 920. https://doi.org/10.3390/medicina61050920.

AlgoTherapeutix. 2025. "A Randomized Double-Blind Placebo-Controlled Crossover Study Evaluating Topical Amitriptyline Hydrogel in Erythromelalgia [Clinical Trial Registration]." ClinicalTrials.gov (NCT05392764). https://clinicaltrials.gov/study/NCT05392764.

Balshem, H., M. Helfand, H. J. Schünemann, et al. 2011. "GRADE Guidelines: 3. Rating the Quality of Evidence." *Journal of Clinical Epidemiology* 64, no. 4: 401–406. https://doi.org/10.1016/j.jclinepi.2010.07.015.

Barker, T. H., S. Hasanoff, E. Aromataris, et al. 2025. "The Revised JBI Critical Appraisal Tool for the Assessment of Risk of Bias for Cohort Studies." *JBI Evidence Synthesis* 23: 441–453. https://doi.org/10.11124/JBIES-24-00103.

Barker, T. H., J. C. Stone, K. Sears, et al. 2023. "The Revised JBI Critical Appraisal Tool for the Assessment of Risk of Bias for Randomized Controlled Trials." *JBI Evidence Synthesis* 21: 494–506. https://doi.org/10.11124/JBIES-22-00430.

Cacciola, R. R., A. Cipolla, E. Di Francesco, R. Giustolisi, and E. Cacciola. 2005. "Treatment of Symptomatic Patients With Essential Thrombocythemia: Effectiveness of Anagrelide." *American Journal of Hematology* 80: 81–83. https://doi.org/10.1002/ajh.20399.

Caldito, E. G., S. Kaul, N. G. Caldito, W. Piette, and S. Mehta. 2024. "Erythromelalgia. Part I: Pathogenesis, Clinical Features, Evaluation, and Complications." *Journal of the American Academy of Dermatology* 90: 453–462. https://doi.org/10.1016/j.jaad.2023.02.071.

Cao, L., A. McDonnell, A. Nitzsche, et al. 2016. "Pharmacological Reversal of a Pain Phenotype in iPSC-Derived Sensory Neurons and Patients With Inherited Erythromelalgia." *Science Translational Medicine* 8, no. 335: 335ra56. https://doi.org/10.1126/scitranslmed.aad7653.

Cook-Norris, R. H., M. M. Tollefson, A. E. Cruz-Inigo, P. Sandroni, M. D. P. Davis, and D. M. R. Davis. 2012. "Pediatric Erythromelalgia: A Retrospective Review of 32 Cases Evaluated at Mayo Clinic Over a 37-Year Period." *Journal of the American Academy of Dermatology* 66, no. 3: 416–423. https://doi.org/10.1016/j.jaad.2011.01.010.

Davis, M. D. P., W. M. O'Fallon, R. S. Rogers, and T. W. Rooke. 2000. "Natural History of Erythromelalgia: Presentation and Outcome in 168 Patients." *Archives of Dermatology* 136: 330–336. https://doi.org/10.1001/archderm.136.3.330.

Dib-Hajj, S. D., A. M. Rush, T. R. Cummins, et al. 2005. "Gain-of-Function Mutation in $Na_v1.7$ in Familial Erythromelalgia Induces Bursting of Sensory Neurons." *Brain* 128: 1847–1854. https://doi.org/10.1093/brain/awh514.

Dib-Hajj, S. D., Y. Yang, J. A. Black, and S. G. Waxman. 2013. "The $Na_v1.7$ Sodium Channel: From Molecule to Man." *Nature Reviews Neuroscience* 14: 49–62. https://doi.org/10.1038/nrn3404.

Ducrocq, M., V. Penalba, L. Castillo, C. Bodemer, C. Greco, and P. Delmas. 2025. "Mepyramine Targets Mutant $Na_v1.7$ Channels to Relieve Pain and Erythema in Primary Erythromelalgia Patients." *Frontiers in Medicine* 12: 1744968. https://doi.org/10.3389/fmed.2025.1744968.

Durosaro, O., M. D. P. Davis, W. M. Hooten, and J. L. Kerkvliet. 2008. "Intervention for Erythromelalgia, a Chronic Pain Syndrome: Comprehensive Pain Rehabilitation Center, Mayo Clinic." *Archives of Dermatology* 144, no. 12: 1578–1583. https://doi.org/10.1001/archdermatol.2008.515.

Eaton, A. C., and H. N. Mayrovitz. 2025. "Primary Erythromelalgia: Historical Perspective and Current Update." *Cureus* 17, no. 2: e78576. https://doi.org/10.7759/cureus.78576.

Fischer, T. Z., E. S. Gilmore, M. Estacion, et al. 2009. "A Novel $Na_v1.7$ Mutation Producing Carbamazepine-Responsive Erythromelalgia." *Annals of Neurology* 65: 733–741. https://doi.org/10.1002/ana.21678.

Geha, P. Y., Y. Yang, M. Estacion, et al. 2016. "Pharmacotherapy for Pain in Inherited Erythromelalgia Based on Functional $Na_v1.7$ Mutation." *Brain* 139: 2713–2725. https://doi.org/10.1093/brain/aww205.

Goldberg, Y. P., N. Price, R. Namdari, et al. 2012. "Treatment of $Na_v1.7$-Mediated Pain in Inherited Erythromelalgia Using a Novel Sodium Channel Blocker." *Pain* 153: 80–85. https://doi.org/10.1016/j.pain.2011.09.008.

Guyatt, G. H., A. D. Oxman, H. J. Schünemann, P. Tugwell, and A. Knottnerus. 2011. "GRADE Guidelines: A New Series of Articles in the Journal of Clinical Epidemiology." *Journal of Clinical Epidemiology* 64, no. 4: 380–382. https://doi.org/10.1016/j.jclinepi.2010.09.011.

Hagedorn, J. M., N. Canzanello, and T. J. Lamer. 2021. "Dorsal Root Ganglion Stimulation for Erythromelalgia Related Foot Pain: A Case Report and Review of the Literature." *Pain Practice* 21: 698–702. https://doi.org/10.1111/papr.12998.

Hao, J., L. Brosse, C. Bonnet, et al. 2021. "The Widely Used Antihistamine Mepyramine Causes Topical Pain Relief Through Direct Blockade of Nociceptor Sodium Channels." *FASEB Journal* 35, no. 12: e22025. https://doi.org/10.1096/fj.202100976RR.

Huang, X., R. Fu, J. Luo, L. Li, Y. Wang, and R. Yang. 2014. "Interferon Alpha-2b Therapy for Myeloproliferative Neoplasms and Erythromelalgia." *Leukemia & Lymphoma* 55: 1460–1465.

Kalgaard, O. M., O. P. F. Clausen, O. J. Mellbye, and T. Hovig. 2003. "Treatment of Erythromelalgia With the Prostacyclin Analogue Iloprost." *Journal of Internal Medicine* 254: 377–382. https://doi.org/10.1046/j.1365-2796.2003.01206.x.

Lee, J. U., J. E. Ma, J. C. Sartori-Valinotti, T. W. Rooke, P. Sandroni, and M. D. P. Davis. 2024. "Procedural Interventions for Erythromelalgia: A Narrative Review." *Vascular Medicine* 29: 723–732. https://doi.org/10.1177/1358863X241279427.

Ma, J. E., J. U. Lee, J. C. Sartori-Valinotti, T. W. Rooke, P. Sandroni, and M. D. P. Davis. 2023. "Erythromelalgia: A Review of Medical Management Options and Our Approach to Management." *Mayo Clinic Proceedings* 98: 136–149. https://doi.org/10.1016/j.mayocp.2022.08.005.

Mann, N., T. King, and R. Murphy. 2019. "Review of Primary and Secondary Erythromelalgia." *Clinical and Experimental Dermatology* 44: 477–482. https://doi.org/10.1111/ced.13891.

Michelerio, A., M. Burlando, A. Herzum, E. Cozzani, and A. Parodi. 2023. "Primary Erythromelalgia: Clinical, Genetic and Therapeutic Features in a Retrospective Case Series." *Dermatology* 239: 542–549. https://doi.org/10.1159/000528749.

Michiels, J. J. 2002. "Aspirin Responsive Thrombotic Complications in Thrombocythemia Vera: A Novel Platelet-Mediated Arterial Thrombophilia." *Turkish Journal of Haematology* 19, no. 2: 225–233.

Michiels, J. J., Z. Berneman, W. Schroyens, and T. Van Joost. 2006. "Erythromelalgia as a Thrombotic Complication of Essential Thrombocythemia and Polycythemia Vera: Response to Aspirin Therapy." *Platelets* 17: 431–436. https://doi.org/10.1080/09537100600701764.

Michiels, J. J., J. P. Drenth, and P. J. Van Genderen. 1995. "Classification and Diagnosis of Erythromelalgia and Erythermalgia." *International Journal of Dermatology* 34: 97–100. https://doi.org/10.1111/j.1365-4362.1995.tb03587.x.

Michiels, J. J., T. Van Joost, V. D. Vuzevski, and J. Abels. 2003. "Erythromelalgia and Thrombocythemia: A Platelet-Mediated Arteriolar Inflammation and Thrombosis Syndrome." *Seminars in Thrombosis and Hemostasis* 29: 393–401. https://doi.org/10.1055/s-2003-44552.

Mørk, C., C. L. Asker, E. G. Salerud, and K. Kvernebo. 2004. "The Prostaglandin Analogue Misoprostol Reduces Symptoms and Microvascular Arteriovenous Shunting in Erythromelalgia." *Journal of Investigative Dermatology* 122: 587–593. https://doi.org/10.1111/j.0022-202X.2004.22236.x.

Munn, Z., T. H. Barker, S. Moola, et al. 2020. "Methodological Quality of Case Series Studies: An Introduction to the JBI Critical Appraisal Tool." *JBI Evidence Synthesis* 18: 2127–2133. https://doi.org/10.11124/JBISRIR-D-19-00099.

Ouzzani, M., H. Hammady, Z. Fedorowicz, and A. Elmagarmid. 2016. "Rayyan—A Web and Mobile App for Systematic Reviews." *Systematic Reviews* 5: 210. https://doi.org/10.1186/s13643-016-0384-4.

Pagani-Estévez, G. L., P. Sandroni, M. D. P. Davis, and J. C. Watson. 2017. "Erythromelalgia: Identification of a Corticosteroid-Responsive Subset." *Journal of the American Academy of Dermatology* 76: 506–511. e1. https://doi.org/10.1016/j.jaad.2016.08.048.

Page, M. J., J. E. McKenzie, P. M. Bossuyt, et al. 2021. "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews." *BMJ* 372: n71. https://doi.org/10.1136/bmj.n71.

Pai, M., A. Iorio, J. Meerpohl, et al. 2015. "Developing Methodology for the Creation of Clinical Practice Guidelines for Rare Diseases: A Report From RARE-Bestpractices." *Rare Diseases* 3, no. 1: e1058463. https://doi.org/10.1080/21675511.2015.1058463.

Pai, M., C. H. T. Yeung, E. A. Akl, et al. 2019. "Strategies for Eliciting and Synthesizing Evidence for Guidelines in Rare Diseases." *BMC Medical Research Methodology* 19: 67. https://doi.org/10.1186/s12874-019-0713-0.

Pfizer. 2019. "Study of PF-05089771 in Erythromelalgia [Clinical Trial Registration]." ClinicalTrials.gov (NCT02167763). https://clinicaltrials.gov/study/NCT02167763.

Poterucha, T. J., W. T. Weiss, R. A. Warndahl, et al. 2013. "Topical Amitriptyline Combined With Ketamine for the Treatment of Erythromelalgia: A Retrospective Study of 36 Patients at Mayo Clinic." *Journal of Drugs in Dermatology* 12, no. 3: 308–310.

Rocca, B., A. Tosetto, G. Petrucci, et al. 2024. "Long-Term Pharmacodynamic and Clinical Effects of Twice- Versus Once-Daily Low-Dose Aspirin in Essential Thrombocythemia: The ARES Trial." *American Journal of Hematology* 99, no. 8: 1462–1474. https://doi.org/10.1002/ajh.27418.

Soliman, N., X. Moisset, M. C. Ferraro, et al. 2025. "Pharmacotherapy and Non-Invasive Neuromodulation for Neuropathic Pain: A Systematic Review and Meta-Analysis." *Lancet Neurology* 24, no. 5: 413–428. https://doi.org/10.1016/S1474-4422(25)00068-7.

St. Olavs Hospital. 2019. "Spinal Cord Stimulation for Refractory Pain in Erythromelalgia [Clinical Trial Registration]." ClinicalTrials.gov (NCT04039633). https://clinicaltrials.gov/study/NCT04039633.

Sun, J., D. D. Ocay, M. Halpin, et al. 2023. "Clinical Characterization of Pediatric Erythromelalgia: A Single-Center Case Series." *Children* 10, no. 8: 1282. https://doi.org/10.3390/children10081280.

Tang, Z., Z. Chen, B. Tang, and H. Jiang. 2015. "Primary Erythromelalgia: A Review." *Orphanet Journal of Rare Diseases* 10: 127. https://doi.org/10.1186/s13023-015-0347-1.

Tham, S. W., and M. Giles. 2018. "Current Pain Management Strategies for Patients With Erythromelalgia: A Critical Review." *Journal of Pain Research* 11: 1689–1698. https://doi.org/10.2147/JPR.S154462.

Tufanaru, C., Z. Munn, E. Aromataris, J. Campbell, and L. Hopp. 2020. "Chapter 3: Systematic Reviews of Effectiveness." In *JBI Manual for Evidence Synthesis*, edited by E. Aromataris and Z. Munn. JBI.

Van Genderen, P. J., and J. J. Michiels. 1997. "Erythromelalgia: A Pathognomonic Microvascular Thrombotic Complication in Essential Thrombocythemia and Polycythemia Vera." *Seminars in Thrombosis and Hemostasis* 23: 357–363. https://doi.org/10.1055/s-2007-996109.

Wang, X., H. Li, Y. Zhang, Y. Zhou, and Y. Wang. 2022. "Stepwise Pharmacological Treatment Strategy for Primary Erythromelalgia Associated With *SCN9A* Variants." *Frontiers in Neurology* 13: 877123. https://doi.org/10.3389/fneur.2022.877123.

Wang, Y., Y. Zhang, X. Chen, L. Wang, and H. Zhou. 2018. "Chemical Lumbar Sympathectomy for Refractory Erythromelalgia: A Prospective Clinical Study." *Journal of Vascular Surgery* 68: 1217–1224. https://doi.org/10.1016/j.jvs.2017.11.078.

Xenon Pharmaceuticals. 2014. "Study of Topical XPF-002 in Erythromelalgia [Clinical Trial Registration]." ClinicalTrials.gov (NCT01741051). https://clinicaltrials.gov/study/NCT01741051.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Search strategy. **Appendix S2:** Study-level risk-of-bias assessment using Joanna Briggs Institute critical appraisal tools. **Appendix S3:** Adverse events reported across included studies. **Appendix S4:** Constitutional SCN9A variants reported in the included studies.