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REVIEW ARTICLE

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Electrical neurostimulation for the treatment of chronic pruritus: A systematic review

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Abstract

Approximately one fifth of the world population experiences continuous itch for 6 weeks or more during their life, that is chronic itch. It is diverse in its aetiologies, and it is notoriously hard to treat. Because itch and pain have largely overlapping pathophysiology and the demonstrated efficacy of neurostimulation in treatment of selected chronic pain conditions, we conducted a systematic review to investigate whether neurostimulation could be an effective treatment for chronic itch. We identified two randomized controlled trials and 17 open label studies or case reports investigating various neurostimulation modalities for the treatment of refractory itch of various aetiologies. Transcutaneous electrical nerve stimulation (TENS) was the most investigated modality ($n = 17$), and in the largest number of conditions. Other modalities were cutaneous field stimulation ($n = 2$), painscrambler ($n = 1$), transcranial direct current stimulation ($n = 1$) and peripheral nerve field stimulation ($n = 1$). Atopic dermatitis was the most studied condition ($n = 5$). Despite the large heterogeneity in used stimulation paradigms and outcome parameters, all studies reported a positive effect of at least one neurostimulation modality. Our review indicates that electrical neurostimulation could be considered for the treatment of refractory chronic itch of selected aetiologies, such as atopic dermatitis or burn pruritus. However, better understanding of the mechanisms of action of the neurostimulation modalities and regimens in various pruritic conditions is necessary.

KEYWORDS
chronic pruritus, itch, neurostimulation, therapy

1 | INTRODUCTION

Pruritus, or itch, is a common symptom of many conditions, dermatological and otherwise (eg internal, neurological or psychiatric). Most often, treatment of itch is targeted at the causative condition.[1,2] In the case of dermatological conditions, topical treatments such as emollients or dermal corticosteroids usually suffice. However, in more severe cases of generalized pruritus, or atopic conditions, treatment with antidepressants, anticonvulsants, biologics, antihistamines or other immune modifiers is not uncommon.[1–3] Nonetheless, there is a substantial proportion of patients who do not respond adequately to these modes of treatment.[4] If, despite treatment, itch persists for 6 weeks or more, it is considered to be chronic.[5]

The similarities between the pathophysiology of itch and pain are evident; both sensations are conducted by unmyelinated C and A delta fibres in response to proinflammatory cytokines and tissue injury, and both can induce peripheral and central sensitization[6] as well as respond to psychological factors[7] and treatment with antidepressants, anticonvulsants or biologics. There have been multiple theories as to what constitutes the pathophysiological difference between itch and pain; currently, the most widely supported is the "labelled-line coding theory".[8,9] However, conclusive evidence does not yet exist.

Various neurostimulation technologies can offer relief for certain intractable chronic pain conditions, which otherwise heavily impact patients' quality of life.[10] The most commonly used electrical neurostimulation modalities are transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS), where the former is performed by the application of external sticker electrodes to the skin, the latter requires the implantation of an electrode lead in the epidural space of the spinal cord. A relative recent invasive method is dorsal root ganglion stimulation (DRGS), where the electrode leads are placed over one or more dorsal root ganglia. Cutaneous field stimulation (CFS) is similar to TENS, with the exception of the presence of small spikes on the sticker electrodes, which penetrate into the epidermis (the rationale being that this would lead to better/more direct stimulation of cutaneous nerves). Less commonly used modalities are peripheral nerve field stimulation (PNFS—where the stimulation electrode is surgically implanted subcutaneously) and transcranial direct current stimulation (tDCS—where electrode-stickers are applied to the cranium directly over the sensorimotor cortices). Research into the mechanisms of action of electrical neurostimulation has provided insight into the pathophysiology of chronic pain and which chronic pain aetiologies are most likely to respond favourably.[11–15]

By analogy with chronic pain and pain associated with neural damage, there is chronic itch and itch associated with neural damage. An example of the latter is postherpetic itch, in which the nervous system is directly involved.[16] However, in many cases, it is not clear to what extent neural injury contributes to itch, and inversely, to what extent chronic itch might cause neurophysiological alterations. Chronic itch is a frequent condition, with a prevalence of nearly 17%,[5] and limited treatment options.[4] Moreover, itch associated with neural damage responds notoriously bad to conventional treatments.[4]

The primary aim of this study was to investigate the evidence of efficacy of electrical neurostimulation in the treatment of chronic itch conditions. Neurostimulation is not part of standard care for patients with chronic itch at the moment. Addition of a new treatment modality might provide new treatment options for patients suffering from refractory chronic itch. Therefore, the secondary aims of this systematic review are assessing which neurostimulation modalities are most effective and which conditions are most likely to respond favourably.

2 | MATERIALS AND METHODS

We performed a systematic review, adhering to a predefined protocol which we uploaded to the PROSPERO register for systematic reviews (#159112). We assessed the existing evidence of effects of neurostimulation for treatment of chronic itch, the different modes of neurostimulation used and the different itch aetiologies for which neurostimulation was used.

2.1 | Inclusion and exclusion criteria

We defined the following inclusion criteria: reports in English had to be available; study design had to be experimental or quasi-experimental; studies had to concern chronic itch; effects of one or several electrical neurostimulation modalities had to be reported. Furthermore, we defined the following exclusion criteria: studies not pertaining to humans; reports published before 1970; congress abstracts, letters or other non-(quasi)experimental designs; studies investigating experimentally or otherwise induced itch.

2.2 | Search protocol

We performed a structured search action on 7 August 2019 of the following databases: Embase, Medline, Web of Science and google scholar. In the development of a structured search action, we were aided by the Erasmus MC medical library.

2.3 | Study selection

All reports identified with our search action were screened by title and abstract and ambiguous results were discussed until agreement was reached (MB, CV). Duplicates were removed, and of those reports deemed matching above stated eligibility criteria, a full-text version was requested. All full-text reports were read. Those meeting the eligibility criteria were used in data synthesis. We did not perform additional searching.

2.4 | Data extraction

We adapted the standard cochrane data collection form for randomized and non-randomized trials into a customized data-extraction sheet, suitable for both randomized and non-randomized (quasi-) experimental studies.[17]

For each article, we recorded methodological features, itch-related outcomes and other relevant data, for example secondary outcomes and adverse events.

2.5 | Assessment of bias

We performed risk of bias assessment whenever possible, using the latest version of the RoB – 2 for randomized controlled trials[18] and ROBINS for non-randomized controlled trials.[19] For the assessment of uncontrolled trials, we used the revised and validated MINORS criteria,[20] as recommended by Fitzpatrick-Lewis et al.[21] For trials

without a control group, the MINORS criteria consist of eight items (clearly stated aim, inclusion of consecutive patients, prospective collection of data, appropriate endpoints, unbiased assessment, appropriate follow-up period, loss to follow-up <5% and prospective study size calculation). For each of these items, a score of 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate) can be assigned. The highest or best possible MINORS score for uncontrolled trials is thus 16, and the lowest possible score is 0.

We used a tool developed by Murad et al.[22] for the assessment of methodological quality of case reports and case series. This tool consists of eight items divided over four categories (selection of patients, ascertainment of exposure and outcome, causality and reporting). For each item, a score is attributed of 0 (inadequate) or 1 (adequate). The highest, or best possible score for case reports and case series is thus 8, and the lowest possible score is 0. We did not use additional sources (next to the reports themselves) to perform risk of bias analysis, or assessment of methodological quality.

2.6 | Outcome measures

We used outcome measures that indicated the effect of neurostimulation on short-term and long-term itch intensity in our data synthesis, for example visual analogue scale (VAS) or numeric rating scale (NRS). Secondary outcome measures were the different modalities and protocols of neurostimulation used and the different aetiologies of itch for which these were used.

If possible, we used relevant summary statistics to represent results; otherwise, we used narrative data synthesis.

3 | RESULTS

Of the 1608 reports that we identified, 37 met our eligibility criteria. Of these 37 reports, 13 were excluded because they were duplicates or because there was no full-text version available.[23–34] After full-text screening of the remaining 24 reports, another five were excluded because they concerned experimentally or otherwise induced itch,[35–37] because they primarily concerned pain,[38] or because they were a letter to the editor[39] (Figure 1).

Nineteen studies were included: two randomized controlled trials (RCT),[40,41] ten uncontrolled trials,[42–51] one case series[52] and six case reports.[53–58]

All studies reported a positive effect of at least one modality of electrical neurostimulation on itch. There was, however, large heterogeneity in methodological set-up and how the effect on pruritus of various aetiologies was measured.

3.1 | Conditions and diseases

All but one report specified one or more itch conditions for which neurostimulation was used. One report[52] described the conditions as "diverse." In total, twenty different itch conditions were reported on. Most studies reported on a single condition (n = 13), while six studies reported on pruritic conditions of multiple aetiologies (Table 1). The condition most frequently investigated, was atopic eczema/atopic dermatitis, by five studies (one trial and four case reports/series). Generalized or senile pruritus, burn pruritus, lichen simplex and notalgia paresthetica were each investigated by three different studies. Table 1 gives a full overview of the different conditions investigated in each study.

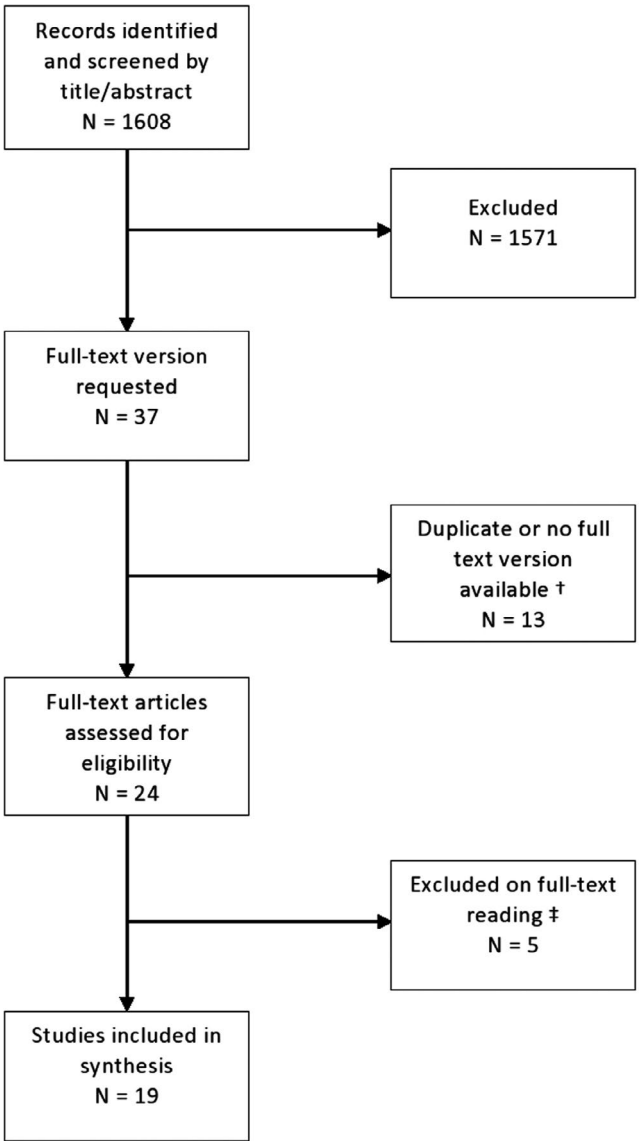

FIGURE 1 Flowchart of study selection. † Congress abstracts (N = 5, Bruel 2013, Lang 2013, Ricciardo 2009, Orthman 2019, Carroll 2009). Only abstract available (N = 3, Fjellner 1978, Kilic Akca 2016, Duo 1987). Only title available (N = 1, Sequeira 2016). Duplicate (N=2, Wallengren 2004, Waked 2013). Erratum (latest version used) (N = 1, Yusek 2013). ‡ Experimentally induced itch (N = 3, Hill 2015, Nilsson 1996, Wallengren 2002). Primarily concerning pain (N = 1, Wang 2009). Letter to editor (N = 1, Tinegate 2002)

3.2 | Neurostimulation modality and stimulation regimen

The included reports studied four different neurostimulation modalities. The majority evaluated the effect of TENS on itch ($n = 15$). The stimulation regimens that were used in these studies, however, were highly variable and are summarized in Table 2.

Duration of treatment varied from a single session of 25 min[41] to 2 years[53]; however, most studies had a treatment duration of one to 4 weeks. Similarly, frequency of treatment varied from three times per day to three times per week, with sessions ranging from 20 min to 1 h (Table 2). Several studies did not report frequency and/or session time. In one study, this was because the stimulation was at the patient's discretion.[45]

The location of stimulation differed between studies and partly depended on the studied condition(s). Almost all the studies concerning localized conditions applied stimulation to the affected or most pruritic area. For generalized conditions, the place of stimulation was variable. Not all studies reported the stimulation settings of the device they used (eg frequency, amplitude).

Two studies evaluated the effect of CFS on itch.[41,50] One was a randomized controlled trial that compared the effect of CFS with the effect of TENS.[41] Furthermore, we identified studies that evaluated the effect of painscrambler therapy,[44] tDCS[55] and PNFS[57] (Table 1).

3.3 | Outcome measures

The most frequently used primary outcome measure to assess the effect of neurostimulation on itch was self-reported VAS for itch intensity ($n = 11$). Several studies used outcome measures comparable to VAS, such as NRS for itch ($n = 2$) or itch intensity measured on a predefined numerical scale ($n = 1$). The remaining five studies did not report itch intensity on any numerical scale or measure, but used descriptive itch intensity relative to baseline. None of the studies mentioned explicitly whether itch measurements applied to discrete time points or to time intervals.

Furthermore, most studies reported on secondary outcomes as well, for example quality of sleep ($n = 4$), multi-dimensional itch instruments (5-D itch scale and Leuven itch scale, which quantify the impact of itch on multiple life domains, $n = 1$), pain ($n = 1$) or dermatological outcome measures ($n = 6$). Lastly, eight studies also reported the occurrence of adverse events as a secondary outcome measure.

The time points at which outcomes were measured varied greatly among studies. Whereas most trials had discrete, predefined time points at which measurements were performed, nearly all case reports lacked these. Table 1 gives an overview of primary outcome measures, and Table 2 gives an overview of the duration of the studies.

3.4 | TENS

All but one of the studies that investigated the effect of TENS on itch found a positive effect. A randomized controlled trial comparing TENS with CFS found that TENS had no significant effect on itch intensity in patients with atopic dermatitis[41]; the overall risk of bias in this study was high, due to a high risk of bias in, among others, the domains of measurement of outcome and selection of reported result.[18]

Positive effect of TENS was reported by nine trials, one of which was an RCT.[40] This randomized controlled pilot study with 30 patients investigated the effect of TENS in patients with burn pruritus. VAS score for itch decreased significantly in the TENS group over 3 weeks of treatment and did not in the control group, who received conventional treatment. Overall risk of bias, however, was high, due to a high risk of bias in, among others, the domains of randomization and selection of reported result.[18]

Furthermore, eight uncontrolled trials,[42,43,45–49,51] four case reports[53,54,56,58] and one case series[52] found a positive effect of TENS on itch intensity. Outcomes of studies investigating TENS are presented in Table 3, and methodological quality/risk of bias assessment are presented in Table 1.

Eight studies aimed to investigate the occurrence of adverse events. One trial with 22 patients with lichen simplex reported a single occurrence of mild erythema during treatment.[43] Another trial with 46 patients with diverse conditions reported eight cases of mild numbness and irritation and 6 cases of mild erythema, all of which were reversible.[46] One trial reported an increase in itch intensity during the application of TENS, though this increased itch did not persist afterwards.[41] Two trials and two case reports also reported improvement in quality of sleep,[45,48,54,56] and three trials reported an improvement in quality of life.[45,49,51]

3.5 | CFS

We identified two trials concerning CFS: an RCT[41] and a trial without a control group.[50] In these trials, 15 patients with atopic dermatitis and 19 patients with diverse conditions were treated with CFS, respectively. Both trials identified a positive effect of CFS on itch. Nilsson et al. found a significant reduction in VAS for itch, lasting up to 7 h after treatment. The risk of bias of this study was high (Table 1). Wallengren et al. found a significant reduction of VAS for itch, at 1–5 weeks of treatment. The methodological quality of this study was assessed using the MINORS criteria, scoring 8 out of 16. Neither of these studies reported on the occurrence of adverse events.

3.6 | Painscrambler

We identified one uncontrolled trial with 16 patients using painscrambler therapy.[44] This modality is similar to TENS; however, it uses different electrical settings, aimed at specifically stimulating C-fibres.[59] This trial reported a significant reduction in NRS for itch after both 5 and 10 days of follow-up. Furthermore, a significant improvement in both 5-D itch scale and Leuven itch scale was noted. Occurrence of adverse events was not reported. The methodological quality of this study was assessed using the MINORS criteria, scoring 12 out of 16.

TABLE 1 Study summary and methodological quality

Study ID	Study type	Neuromodulation	Number of patients	Conditions	Primary outcome	Risk of bias/ quality[a]
Hettrick (2004)	Pilot-RCT	TENS	30	Burn pruritus	VAS for itch	RoB-2: High risk of bias
Nilsson (2004)	RCT	CFS, TENS	35	Atopic dermatitis	VAS for itch	RoB-2: High risk of bias
Bicer (2003)	Trial	TENS	15	Generalized pruritus	VAS for itch	MINORS: 8
Engin (2009)	Trial	TENS	22	Lichen simplex	VAS for itch	MINORS: 10
Joo (2017)	Trial	Painscrambler	16	Burn pruritus	NRS for itch	MINORS: 12
Lyon (1998)	Trial	TENS	24	Psoriasis ($n = 12$), eczema ($n = 7$), lichen planus ($n = 1$), mycosis fungoides ($n = 1$), pemphigoid ($n = 1$), pruritus vulvae ($n = 1$), senile/idiopathic pruritus ($n = 1$)	VAS for itch	MINORS: 8
Mohammad (2015)	Trial	TENS	46	Atopic dermatitis ($n = 10$), lichen simplex chronicus ($n = 20$), chronic liver disease ($n = 16$)	VAS for itch	MINORS: 10
Savk (2007)	Trial	TENS	15	Notalgia paraesthetica	NRS for Itch	MINORS: 10
Tang (1999)	Trial	TENS	5	astheatotic eczema ($n = 1$), plantar eczema ($n = 1$), prurigo nodularis ($n = 1$), atopic eczema ($n = 1$), neurodermatitis ($n = 1$)	VAS for itch	MINORS: 12
Waked (2019)	Trial	TENS	33	Lichen planus	VAS for itch	MINORS: 10
Wallengren (2001)	Trial	CFS	19	Brachioradial pruritus ($n = 9$), mycosis fungoides ($n = 1$), notalgia paraesthetica ($n = 5$), neurodermatitis ($n = 1$), meralgia paraesthetica ($n = 1$)	VAS for itch	MINORS: 8
Yusek (2011)	Trial	TENS	16	Macular amyloidosis ($n = 8$), lichen simplex ($n = 8$)	VAS for itch	MINORS: 10
Bjorna (1987)	Case report	TENS	1	Atopic eczema	Itch intensity on 6-point scale	Murad: 7
Carlsson (1975)	Case series	TENS	17	Diverse (not further specified)	Itch intensity (not further specified)	Murad: 2
Chan (2000)	Case report	TENS	2	Reactive perforating collagenosis	Itch intensity (not further specified)	Murad: 4
Knotkova (2013)	Case report	tDCS	1	Syringomyelia	Itch intensity (relative to baseline)	Murad: 8
Monk (1993)	Case report	TENS	2	Generalized pruritus	Itch intensity (not further specified)	Murad: 5
Ricciardo (2010)	Case report	PNFS	1	Notalgia paraesthetica	Itch intensity (not further specified)	Murad: 2
Whitaker (2001)	Case report	TENS	1	Burn pruritus	VAS for itch	Murad: 6

Abbreviations: CFS, Cutaneous Field Stimulation; NRS, Numerical Rating Scale; PNFS, Peripheral Nerve Field Stimulation; tDCS, transcranial Direct Current Stimulation; TENS, Transcutaneous Electrical Nerve Stimulation; VAS, Visual Analog Scale.

[a]RoB-2 for RCT's: high, medium or low risk of bias; MINORS for uncontrolled trials (worst – best): 0–16; Murad et al. for case reports and case series (worst – best): 0–8.

TABLE 2 Stimulation regimen

Study ID	Neuromodulation	Duration of treatment	Stimulation regimen	Stimulation settings
Hettrick (2004)	TENS	3 weeks	Daily session of 1 h	High-frequency, low intensity
Nilsson (2004)	TENS	1 session	Single session of 25 min	Pulse: 0.2 ms Amplitude: 10–26 mA Frequency: 100 Hz
	CFS			Pulse: 1.0 ms Frequency: 4 Hz
Bicer (2003)	TENS	3 weeks	1-h sessions, usage not specified	Pulse: 0.25 ms Frequency: 2–120 Hz
Engin (2009)	TENS	4 weeks	3 sessions of 1 h per week	High frequency, low intensity Pulse: ≤0.1 ms Frequency: ≥100 Hz
Joo (2017)	Painscrambler	Not specified	Not specified	NS
Lyon (1998)	TENS	1 week	Not specified	Pulse: 0.2 ms Frequency: 50–100 Hz
Mohammad (2015)	TENS	4 weeks	Up to 3 sessions of 30 min per week	Pulse: 0.04–0.075 ms Frequency: 50–100 Hz
Savk (2007)	TENS	2 weeks	5 sessions of 20 min per week	Pulse: 0.04–0.075 ms Frequency: 50–100 Hz
Tang (1999)	TENS	1 week	Daily session of at least 1 h, then continued up to itch reduction	Pulse: 0.2 ms Frequency: 80–100 Hz
Waked (2019)	TENS	4 weeks	3 sessions of 1 h per week	Frequency: 100 Hz
Wallengren (2001)	CFS	5 weeks	Daily session of 20–30 min	Not specified
Yusek (2011)	TENS	4 weeks	3 sessions of 30 min per week	Pulse: 0.04–0.075 ms Frequency: 50–100 Hz
Bjorna (1987)	TENS	2 years	Decreasing over a 2-year period from 3 sessions of 30 min per day to sporadic sessions.	Bursts: 5 pulses at 100 Hz Amplitude: 15–30 mA Frequency: 2 Hz
Carlsson (1975)	TENS	Not specified	Sessions of 1–2 min, usage not specified	Pulse: 0.2 ms Frequency: 60 Hz
Chan (2000)	TENS	3 weeks	Daily session of 1 h	Not specified
Knotkova (2013)	tDCS	5 days	Daily session of 20 min	SI: cathodal inhibitory, 2 mA; MI: anodal excitatory, 2 mA, anodal excitatory, 2 mA
Monk (1993)	TENS	Not specified	Not specified	Pulse: 0.2 ms Amplitude: 50 mA Frequency: 15–175 Hz
Ricciardo (2010)	PNFS	5 months	Continuous	Not specified
Whitaker (2001)	TENS	3 weeks	Average daily stimulation time of 9 h, duration of sessions not specified	Amplitude: 5–8 mA

Abbreviations: CFS, cutaneous field stimulation; NRS, Numerical Rating Scale; PNFS, peripheral nerve field stimulation; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; VAS, Visual Analog Scale.

3.7 | tDCS

We identified one case report on tDCS in a patient suffering from syringomyelia.[55] The patient reported a 50–60% improvement in itch intensity, relative to baseline, which lasted up to 3 months after treatment. NRS for pain was reported as well, since treatment was originally intended for neuropathic pain. Pain was, however, not affected by the treatment. Occurrence of adverse events was not reported. The methodological quality of this case report was assessed using the tool by Murad et al., scoring 6 out of 8.

3.8 | PNFS

We identified one case report applying PNFS to a 60-year-old woman with intractable notalgia paresthetica.[57] Postimplantation of the subcutaneous PNFS electrode, the patient described an 85% reduction of itch intensity, compared to baseline. This effect was maintained for at least 5 months. Occurrence of adverse events was not reported. The authors concluded that PNFS is a possible treatment for unresponsive notalgia paraesthetica. The methodological quality of this case report was assessed using the tool by Murad et al., scoring 2 out of 8.

TABLE 3 Main results of studies investigating transcutaneous electrical nerve stimulation

Study ID	Outcome	Time points for evaluation	Reported as[a]	Result	*p*-value	Adverse events
Hettrick (2004)	VAS for itch	Daily	Slope	TENS: −3.51	<0.02	–
Nilsson (2004)	VAS for itch	8 measurements up to 12 h after treatment	Description[b]	During treatment: +409% No significant reduction in VAS for itch up to 12 h after treatment	<0.01 >0.05	–
Bicer (2003)	VAS for itch	3, 7, 15 and 21 days after start of treatment	Slope	Day 3: 7.13 Day 7: 5.0 Day 15 3.93 Day 21: 2.93	<0.001	No
Engin (2009)	VAS for itch	1 and 2 months after start of treatment	Difference	Baseline: 7 1 month: 2.5 2 months: 2.54	NA <0.01 <0.01	Yes
Lyon (1998)	VAS for itch	7 days after start of treatment	% reduction	35.4%	<0.05	No
Mohammad (2015)	VAS for itch	2 weeks, 1 and 2 months after start of treatment	Difference	Baseline AD: 7.1; LSC: 7.7; CLD: 7.1 2 weeks AD: 4.5; LSC: 4.9; CLD: 4.8 1 month AD: 1.8; LSC 2.5; CLD: 2.8. 2 months AD: 2.7; LSC 3.3; CLD: 4.0.	NA <0.001 <0.001 <0.001	Yes
Savk (2007)	NRS for Itch	1 and 2 weeks after start of treatment	Difference	1 week: 7.67 2 weeks: 6.8	<0.05 <0.05	No
Tang (1999)	VAS for itch	Daily measurements for 7 days	Mean	Day 1: 7 Day 2: 5 Day 3: 5 Day 4: 4 Day 5: 4 Day 6: 4 Day 7: 4	NR	No
Waked (2019)	VAS for itch	2 and 4 weeks after start of treatment	Difference	Baseline: 8.3 2 weeks: 5.63 4 weeks: 2.13	NA NR <0.001	No
Yusek (2011)	VAS for itch	2 and 4 weeks after start of treatment	Difference	Baseline: 8 2 weeks: 4 4 weeks: 2	NA <0.001 <0.001	–
Bjorna (1987)	Itch intensity on 6-point scale	Daily measurements for 8 months	Modus	Baseline: 4 1–4th month: 1 4–5th month: 2 6th month: 1 7–8th month: 0	NA	–
Carlsson (1975)	Itch intensity (not further specified)	Not reported	Description[b]	"14 out of 17 patients experienced considerable alleviation of itch."	NA	–
Chan (2000)	Itch intensity (not further specified)	Not reported	Description[b]	"Both patients experienced substantial relief of itch."	NA	No
Monk (1993)	Itch intensity (not further specified)	Not reported	Description[b]	Abolition of itch after several sessions; one patient reported prolonged itch reduction.	NA	–

(Continues)

TABLE 3 (Continued)

Study ID	Outcome	Time points for evaluation	Reported as[a]	Result	*p*-value	Adverse events
Whitaker (2001)	VAS for itch	Daily measurements for 3 weeks	Description[b]	Progressive reduction over a 3-week period in itch pre-, immediately after, and 4 h post-treatment.	NA	–

Abbreviations: AD, atopic dermatitis; CLD, chronic liver disease; LSC, lichen simplex chronicus; NA, not applicable; NR, not reported; NRS, Numerical Rating Scale; VAS, Visual Analog Scale.

[a]Differences are relative to baseline, unless otherwise specified.

[b]Only descriptive results were provided.

3.9 | Secondary results

Several studies reported dermatological, pathological or biochemical parameters as secondary results. A trial investigating TENS reported a significant healing effect in only a minority of patients (8 out of 22).[43] Another trial of 33 patients with TENS reported a significant improvement in Dermatological Quality of Life Index (DQLI) ($p < 0.001$) after 2 weeks of treatment.[49] A similar finding was reported in a study investigating TENS in patients with macular amyloidosis and lichen simplex, both groups showed a significant improvement in DQLI after 2 weeks of treatment ($p = 0.001$, $p = 0.006$, resp.).[51] A case report concerning a patient with atopic dermatitis furthermore reported influence of TENS on plasma levels of adrenocorticotrophic hormone (ACTH) and vasoactive intestinal peptide (VIP) as markers for inflammation and disease activity, as well as rise in skin temperature and clinical improvement of lesions.[53] One study investigating the effect of CFS in patients notalgia paraesthetica and brachioradial pruritus used skin biopsies to determine the density of cutaneous nerve fibres. No significant alteration in nerve fibre density was observed, however.[50]

4 | DISCUSSION

There is evidence that certain electrical neurostimulation modalities can effectively treat refractory chronic itch. However, the studies we identified were mostly of low methodological quality or provided merely a low level of evidence (eg case reports). All studies reported a positive effect of at least one neurostimulation modality on chronic itch, but neurostimulation modalities and causes of itch varied largely. We therefore conclude that although there are indications that neurostimulation can be an effective treatment for chronic itch of selected aetiologies, additional research is needed to further optimize and establish neurostimulation as a treatment for chronic itch.

We found notably more studies relating to the effect of TENS than to any other neurostimulation modality. Though the evidence suggesting a positive effect of TENS in the treatment of chronic itch is stronger and more abundant, even the largest trials we identified had several methodological drawbacks. Furthermore, among the two studies supplying the highest level of evidence, there was no consensus regarding the effectivity of TENS. This could be due to the high variety in stimulation regimens that were used (eg duration, frequency and settings). None of the studies provided justification or explanation for the specific regimens that were used. Regarding the other modes of neurostimulation we identified (PNFS, pain-scrambler, CFS and tDCS), there are only tentative indications of positive effects. CFS was second most studied, by two trials, one of which was an RCT. However, analogous to TENS, there were similar methodological drawbacks to both studies.

The most prominent limitations of our systematic review are the limited number of large, methodologically sound studies and that the conducted studies showed large heterogeneity with regard to duration, stimulation regimen and the moments at which the effect of stimulation was assessed. It was therefore not feasible to perform a meta-analysis. The fact that all the studies we identified reported a positive effect of at least one neurostimulation modality might also in part be due to publication bias.

5 | MAJOR OPEN QUESTIONS

Though our systematic review provides an indication that electrical neurostimulation is beneficial for certain patients suffering from chronic itch, several points require further research. As mentioned, there is a lack of large, methodologically sound trials. In order to further establish the efficacy of modalities such as TENS for the treatment of chronic itch, such trials are imperative. Furthermore, based on the current evidence, it is not possible to recommend a specific stimulation regimen. Different regimens need to be compared in a systematic and prospective fashion.

The itch conditions for which TENS and other electrical neurostimulation modalities were applied were very diverse, ranging from common conditions such as atopic dermatitis, to rarer ones, as for instance notalgia paraesthetica. However, all studied itch conditions concerned localized dermatologic or neuropathic itch conditions. For generalized itch or systemic itch, we did not find evidence, which suggests that their treatment with neurostimulation possibly has to be more invasive to target more central structures. Based on the current evidence, it is not possible to reliably predict the response to a specific neurostimulation treatment for the various itch conditions. All the investigated conditions responded to at least one neurostimulation modality, even though most did not have a clear neuropathic

origin, but were rather chronic pruritic dermatoses. This observation underlines the necessity of further research into the neurophysiology and pathophysiology of various chronic itch conditions and the working mechanisms of neurostimulation in chronic itch.

6 | CONCLUSIONS AND PERSPECTIVES

Our review indicates that neurostimulation (especially TENS) can be considered as a treatment option for patients with intractable pruritus. Furthermore, the beneficial effect of electrical neurostimulation in pruritic dermatoses such as atopic dermatitis provides an indication (albeit circumstantial) that there is a neurogenic component in the pathophysiology of these conditions that can be targeted.

The use of electrical neurostimulation has proved to be a useful option in the treatment of chronic pain. Future research will have to further establish and optimize the role of electrical neurostimulation in the treatment of chronic itch. Though the analogy to pain would suggest that neurostimulation should be of great use to those pruritic conditions that involve direct damage to the nervous system, our study shows that neurostimulation might very well have a wider use, including primary pruritic dermatoses.

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CONFLICT OF INTEREST

All authors declare they have no affiliations with or involvement in any organization or entity with any financial interests, or non-financial interests in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTIONS

The conception originated from C.C. de Vos. The protocol was written by M. Badwy. Articles were selected by M. Badwy and C.C. de Vos. Subsequent data extraction and analysis was performed by M. Badwy, S.J. Baart and C.C. de Vos. The first draft was written by M. Badwy, and further input was provided by H.B. Thio, F.J.P.M. Huygen and C.C. de Vos.

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