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INVESTIGATIVE REPORT

Psychophysiological Processing of Itch in Patients with Chronic Post-burn Itch: An Exploratory Study

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A substantial proportion of patients with burn injury develop chronic itch, which can severely affect their quality of life. As found in research on chronic pain, different psychophysiological processes may also play a role in chronic itch, of which central sensitization, conditioned modulation, and attentional processes have been studied most frequently. This study aimed to explore psychophysiological processes of chronic post-burn itch by comparing 15 patients with long-term itch due to burn injury with 15 matched healthy controls. Exploratory results indicated tendencies for higher itch sensitivity in patients than in controls, for mechanical stimuli and histamine, but not for electrical stimulation. Results further suggest that the efficacy of itch modulation by an itch- or pain-conditioning stimulus or directing attention towards itch stimuli do not differ between these patients and controls. Further elucidation of the processes underlying post-burn itch may improve the early identification and treatment of burn patients developing chronic itch.
Key words: pruritus; itch; burn wounds; sensitization; itch modulation; quantitative sensory testing.

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Itch is a common sensation following skin burns, and is reported by 93% of patients following burn injury (1, 2). Itch is most severe in the first months after wound closure, after which spontaneous itch gradually subsides (1, 2). However, even 2 years after burn injury 67–73% of patients, in particular those with a larger total body surface area affected, still report mild to severe levels of itch (1). When all phases of wound healing have been completed, itch is termed "chronic" (3). Chronic itch has serious consequences for the patient's well-being and functioning in daily life (2, 4). The pattern of decline in itch varies widely between patients, and several burn injury-related and individual factors have been shown to be risk factors for chronic itch, e.g. post-traumatic stress (2, 4). The pathophysiology of chronic post-burn itch is largely unknown (1, 3). In the acute phase of burn injury itch is assumed to be based on an increase in inflammatory mediators, including histamine, and neuronal damage (1, 3). However, these processes do not fully account for chronic post-burn itch, e.g. antihistamines only provide certain relief for a proportion of patients, and therefore central psychophysiological processes may also play a role (1, 3).

Psychophysiological processes may play a role in spontaneous itch when symptoms no longer directly reflect the input from peripheral nerve fibres (5). These processes have mostly been studied with regard to chronic pain, and have recently also been suggested to play a role in chronic itch. Central and peripheral sensitization (5, 6), impaired conditioned pain modulation (CPM) (7), and attentional processes (8, 9) have been studied most frequently. With central and peripheral sensitization, structural neuroplastic changes occur that result in an amplification of nociceptive signals in the central nervous system. This has been demonstrated by studies showing that patients with chronic itch due to inflammatory dermatoses, e.g. atopic dermatitis, generally seem to display heightened sensitivity to itch stimuli and perceive painful stimuli as itching (5, 10, 11). However, it should be noted that there is also contradictory evidence regarding the notion of sensitization in patients with chronic itch (12, 13). In addition, endogenous modulation has frequently been investigated with regard to pain in a conditioned pain modulation (CPM) paradigm, by showing that pain can be inhibited by a secondary, heterotopically applied pain stimulus, i.e. pain inhibits pain. CPM efficacy has been shown to be impaired in patients with chronic pain (7). Similarly, there are indications that conditioned itch modulation (CIM) efficacy, i.e. inhibition of itch by a heterotopic itch stimulus, is impaired in patients with chronic itch due to psoriasis (14). Finally, attentional processes can

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also play a role in the amplification of symptoms. In chronic pain, a heightened selective (maintained) attention to pain and related stimuli, e.g. assessed with words, is assumed to play a role in spontaneous pain (8, 9). Preliminary evidence in patients recovered from burn wounds, compared with control subjects, shows that patients display more selective attention to burn-related words, including scars, burn injury, and itch (15), although this study did not specifically focus on burn patients with itch. In addition, self-reported attention has been related to itch sensitivity in healthy subjects (16).

On the basis of the research discussed above, it might be expected that patients with long-term post-burn itch would display heightened sensitivity to itch stimuli, impaired conditioned itch modulation, and heightened selective attention towards itch stimuli compared with healthy subjects. However, these psychophysiological processes have not been explored in patients with chronic itch due to burn wounds. Therefore, the aim of this study is to explore these processes regarding itch in this patient group in comparison with healthy subjects. In addition, the role of individual characteristics, such as psychological distress (e.g. post-traumatic stress) and personality characteristics (e.g. neuroticism), in the psychophysiological processing of itch will also be explored. Knowledge obtained from this study can be used in future studies to focus more specifically on psychophysiological processes particularly relevant in post-burn itch. In time, more insight into the psychophysiological mechanisms of chronic post-burn itch, e.g. obtained from longitudinal studies directed to identify specific biomarkers predicting chronic itch, can contribute to improve treatment of post-burn itch, and hence, the quality of life of burn-injured patients.

METHODS

Participants

Fifteen adult patients with long-term itch following burn injuries and 15 adult healthy controls, matched for sex and age (maximum 6 years deviation) were included in the study. Patients were included when having spontaneous itch for at least 6 months after burn injury (2, 3). Subjects aged ≥ 18 years with sufficient understanding of the Dutch language were included. Exclusion criteria were: chronic itch or pain of medical cause other than burn wounds, multiple sclerosis, insulin and non-insulin dependent diabetes, diagnosis of histamine hypersensitivity, psychotic disorders, or other psychopathology unrelated to the burn injury, use of pacemaker, epilepsy, claustrophobia, pregnancy, colour-blindness, or having extensive injuries of the soft tissue of the face and the head that could interfere with the electroencephalography (EEG) measurements. Patients were also excluded when the location of the burn scars did not allow application of the somatosensory itch stimuli on unaffected (non-scarred) skin. All participants had normal or corrected-to-normal vision, with the exception of one patient, who had Fuchs' corneal dystrophy; this patient reported that this had not obstructed him in his performance during the tests. One of the patients reported during screening that she had a diagnosis of Raynaud's phenomenon, and thus this patient did not perform the cold pressor task (CPT). Patients were recruited through advertisements by the Dutch Burns Foundation and the Dutch Association of Burn survivors. Healthy subjects were recruited by an advertisement on a national website for the recruitment of research participants.

General procedure

The protocol was approved by the Medical Ethics Review Committee CMO Regio Arnhem-Nijmegen. The board of the Leiden University Medical Center (LUMC) gave permission for the study to be carried out in the LUMC (Department of Psychiatry). The study was conducted according to the protocols of the Declaration of Helsinki. Potential participants were informed by written information and, if interested, they were screened with a short telephone interview. In case of doubt about inclusion of a participant, a medical doctor was consulted. Eligible subjects received questionnaires approximately 2 weeks before their appointment. Patients and healthy subjects were both asked about demographic characteristics. Patients completed questions related to the burn incident, e.g. about the localization of itch (degree of itch inside vs. outside the burn scars), the cause of burn injury, the total body surface area affected, how many years ago the burn incident took place, and the length of hospital stay directly after the incident. In addition, several self-report questionnaires, which have previously been shown to have satisfactory reliability and validity, were administered in Dutch (see Appendix S1[1] – Questionnaires).

On the day of testing, after explaining the test procedure, written informed consent was obtained from each participant. First, participants completed some additional questionnaires assessing mood state (see Appendix S1[1] – Questionnaires). Secondly, computer tasks were conducted in the following order: the approach avoidance task measuring behavioural reactions regarding itch, the name letter task measuring self-esteem (to be presented in another paper), and the Stroop task modified for itch measuring selective attention to itch (see Appendix S1[1] – Computer tasks measuring automatic reactions to itch). Thirdly, participants were prepared for the EEG measurements (to be presented in another paper). Thereafter, EEG was measured during rest, and, subsequently, somatosensory stimuli inducing itch or pain were applied to investigate both sensitivity towards itch stimuli and CIM. To this end, mechanical, electrical, and histamine stimuli were applied to investigate sensitivity to itch (10, 11, 17, 18). Histamine was also used as conditioning stimulus as part of the CIM procedure investigating the inhibition of electrically induced itch by itch (14). In addition, as part of a CIM procedure investigating the inhibition of electrically induced itch by pain, a CPT was applied as painful conditioning stimulus; see Appendix S1[1] for a detailed description of the procedures. During the test, there were several standard breaks and subjects were told they could request additional breaks at any time. Subjects were instructed not to scratch during the measurements. Participants were compensated for travel expenses and received gift vouchers. Data analyses mainly involved comparing the groups (patients vs. healthy controls) on the levels of itch induced by the somatosensory stimuli, efficacy of itch modulation by both an itch and painful stimulus, and automatic attention for itch-related words. Individual characteristics were descriptively reported when burn injury-related, and compared between groups when assessing general characteristics. The effects of patients' post-traumatic stress on the outcome measures were explored. For a detailed description of the methods and analyses, see Appendix S1[1].

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RESULTS

Participants

Table I displays the individual characteristics (demographics and questionnaires) of the patients with chronic post-burn itch and the healthy controls included in this study. There were no significant differences between the groups with regard to age, sex, and education level. Medication was used in the 24 h prior to testing by one healthy subject (medication for high blood pressure) and 6 patients (i.e. a selective serotonin reuptake inhibitor (SSRI) and benzodiazepine ($n = 1$), paracetamol ($n = 1$), non-steroidal anti-inflammatory drug ($n = 1$), inhalation medication because of burn injuries in the lungs ($n = 1$), statin and SSRI ($n = 1$), proton pump inhibitor, medication for mild asthmatic bronchitis, and medication for urinary retention ($n = 1$)).

The burn incident had occurred in a mean of 19.8 (standard deviation (SD) 18.0) years previously (range 2.4–64.7 years) and the self-reported total body surface area affected was 27.4% (SD 18.6) with a range of 3–68%. Directly after the burn incident, patients had stayed in a hospital for a mean of 21.9 (SD 19.9) weeks (range 0.2–24 weeks). The causes of the burn injury were fire/burning gel ($n = 10$), fireworks ($n = 1$), hot liquids ($n = 2$), chemicals ($n = 1$) and electrocution ($n = 1$).

The Burn Itch Questionnaire showed that the burn scars were widely distributed across the body. Of the patients, 67% had burns on the thorax/abdomen, 40% on the head/neck, 40% on the hands, 27% on the legs/buttock, 20% on the arms, 13% on the feet, and 7% on the genitals. Although these data do not enable exact localization of the burn injury within specific dermatomes, an estimate was made of whether the itch stimuli were applied within dermatomes that were, ipsilaterally or contralaterally, affected by burn scars (though itch stimuli were applied to non-affected skin). Dermatomes were ipsilaterally and contralaterally affected in 40% and 27% of patients, respectively, for mechanical stimulation; in 53% and 27% of patients, respectively, for electrical stimulation; and in 60% and 20% of patients, respectively, for histamine. In only one patient were all stimuli applied in unaffected dermatomes. With regard to the localization of itch, 23% of patients reported the itch to be located only in the burn scars, 61% reported itch to be located mainly in the burn scars and minimally on other body areas, 8% reported itch to be distributed equally over areas located in the burn scars and unaffected body areas, and 8% of patients reported the itch to be located mainly outside the burn scars. With regard to the individual characteristics (see also Table I), the levels of psychological distress, affect, neuroticism, extraversion, and attentional focusing on bodily sensations were not significantly different between groups (all $p > 0.05$). Nine patients had no post-traumatic stress according to the Impact of Event Scale (IES), while 6 patients had clinically relevant post-traumatic stress (IES score ≥ 26) (19).

Table I. *Participants' individual characteristics*

	Patients with post-burn itch	Healthy subjects
Age, years, mean (SD); range	41.6 (14.7); 18.4–66.7	41.0 (13.0); 21.1–60.6
Sex, F/M, *n*	10/5	10/5
Education level: secondary/tertiary, %	53/47	60/40
Levels of itch at baseline, mean (SD); range	2.8 (2.6); 0.0–8.0	0.1 (0.3); 0.0–1.0
Levels of itch past 4 weeks, mean (SD); range	5.2 (2.2); 1.4–8.0	1.0 (0.8); 0.0–2.5
Burn-specific health (BSHS-B), mean (SD)	28.6 (5.2)	NA
Burn-related itch (BIQ), mean (SD)		
Itch intensity subscale	5.1 (2.3)	NA
Interference sleep subscale	3.2 (2.4)	NA
Interference daily life subscale	2.5 (1.8)	NA
Burn scar quality (patients scale of POSAS), mean (SD)	38.7 (9.9)	NA
Post-traumatic stress (IES), mean (SD)	23.0 (21.8)	NA
Intrusion subscale (IES-I)	10.6 (9.1)	NA
Avoidance subscale (IES-A)	12.4 (13.9)	NA
Psychological distress (HADS), mean (SD)		
Anxiety subscale	5.5 (3.4)	3.9 (2.4)
Depression subscale	3.7 (3.9)	2.7 (2.3)
Affect (PANASs), mean (SD)		
Positive affect subscale	15.9 (4.5)	17.3 (3.5)
Negative affect subscale	7.8 (4.3)	5.8 (1.5)
Personality characteristics (EPQ-RSS), mean (SD)		
Neuroticism subscale	4.8 (3.3)	3.0 (2.1)
Extraversion subscale	8.9 (2.9)	9.9 (1.9)

Theoretical range of questionnaires: Brief Burn Specific Health Scale (BSHS-B): 0–160; Burn Itch Questionnaire (BIQ): all subscales 0–36; Patient and Observer Scar Assessment Scale (POSAS): 0–60; Impact of Event Scale (IES): 0–75; IES-I 0–35; IES-A 0–40; Hospital Anxiety and Depression Scale (HADS): both subscales 0–21; Positive and Negative Affect Schedule short version (PANASs): both subscales 5–25; Eysenck Personality Questionnaire Revised short scale (EPQ-RSS): both subscales 0–12.
NA: not applicable; F: female; M: male; SD: standard deviation.

Sensitivity to itch stimuli

Mean levels and SD of itch evoked by the different somatosensory stimuli are shown in Table II. Mechanical stimulation evoked itch in 5 healthy subjects and 11 patients. In one healthy subject, impedance was too high to adequately measure the electrical itch tolerance threshold; therefore the means of 14 healthy subjects are reported. One patient terminated the hista-

Table II. *Mean (SD) scores of itch evoked by the somatosensory stimuli applied (scored on an NRS ranging from 0 to 10)*

	Patients with post-burn itch Mean (SD)	Healthy controls Mean (SD)
Monofilaments	0.8 (0.9)	0.4 (0.7)
Electrical itch tolerance threshold (IT3)[a]	4.0 (2.8)	3.6 (2.2)
Histamine iontophoresis	4.2 (2.2)	2.8 (1.9)

[a]Defined by the first moment you cannot resist the urge to scratch.
SD: standard deviation; NRS: numerical rating scale.

mine application prematurely because of experiencing high levels of itch. Results indicated trends towards significance for higher levels of itch in the patients compared with the healthy subjects for the mechanical stimulation ($F(1,28) = 3.27$, $p = 0.081$; partial $\eta^2 = 0.105$, 90% confidence interval (CI) 0.00–0.29) and histamine ($F(1,28) = 3.15$, $p = 0.087$; partial $\eta^2 = 0.101$, 90% CI 0.00–0.28), and no significant between-group difference for itch evoked at the electrical itch tolerance threshold ($F(1,27) = 0.009$, $p = 0.926$; partial $\eta^2 = 0.001$, 90% CI 0.00–0.01). A non-parametric test for mechanical stimulation obtained similar results ($U = 69$, $p = 0.057$).

Conditioned itch modulation by itch and pain stimuli

The repeated measures analysis of variance (ANOVA) for testing CIM efficacy by the heterotopically applied histamine itch stimulus (see Fig. S1A[1]) showed that the levels of itch evoked by electrical test stimuli were significantly reduced after, compared with before, histamine ($F(1,28) = 4.90$, $p < 0.05$; partial $\eta^2 = 0.15$, 90% CI 0.01–0.34). There was no significant interaction effect for time × condition ($F(1,28) = 0.08$, $p = 0.78$; partial $\eta^2 = 0.003$, 90% CI 0.00–0.09), indicating that CIM efficacy did not differ between patients and controls. Similarly, CIM efficacy by the heterotopically applied pain stimulus (see Fig. S1B[1]) showed that itch levels evoked by electrical stimulation significantly reduced after, compared with before, the CPT ($F(1,27) = 9.65$, $p < 0.01$; partial $\eta^2 = 0.26$, 90% CI 0.05–0.45). There was no significant interaction effect for time × condition ($F(1,27) = 0.27$, $p = 0.61$; partial $\eta^2 = 0.01$, 90% CI 0.00–0.13), indicating that CIM efficacy did not differ between patients and controls. In addition, mean pain evoked by the CPT did not significantly differ between patients (4.4, SD 3.0) and controls (3.2, SD 2.5) ($F(1,27) = 1.31$, $p = 0.26$), but immersion times were significantly shorter for the patients than for the controls ($F(1,27) = 4.53$, $p < 0.05$).

Selective attention to itch

The mean reaction times for the different word categories in the modified Stroop task are displayed in Table III. There was a significant main effect for word category ($F(3,26) = 4.36$, $p < 0.05$; partial $\eta^2 = 0.33$, 90% CI 0.05–0.47). Simple contrasts showed overall significant differences in the reaction time for naming the colours of the itch words in comparison with the neutral words ($F(1,28) = 7.42$, $p < 0.05$; partial $\eta^2 = 0.21$, 90% CI 0.03–0.40) and positive words ($F(1,28) = 11.27$, $p < 0.01$; partial $\eta^2 = 0.29$, 90% CI 0.07–0.47), but not with the negative words ($F(1,28) = 0.34$, $p = 0.57$; partial $\eta^2 = 0.01$, 90% CI 0.00–0.14).There was no significant interaction effect of word category × condition ($F(3,26) = 0.32$, $p = 0.81$; partial $\eta^2 = 0.04$, 90% CI 0.00–0.11), indicating that attentional processes did not differ between patients and healthy controls.

Table III. *Modified Stroop task: colour-naming reaction times in seconds per word category for the patients with chronic itch due to burn wounds and healthy controls*

	Patients with post-burn itch Mean (SD)	Healthy subjects Mean (SD)
Itch words	30.7 (6.4)	31.7 (6.2)
Neutral words	29.4 (6.7)	29.7 (6.2)
Positive words	29.1 (6.3)	29.7 (5.6)
Negative words	30.9 (7.4)	30.7 (6.6)

SD: standard deviation.

Comparison of patients with and without post-traumatic stress

From inspection of the data, descriptive results showed that the patients with post-traumatic stress, in comparison with the patients without post-traumatic stress, displayed considerably higher levels of itch due to histamine (mean 4.9 (SD 2.3) vs. mean 3.6 (SD 2.1), respectively), an increase (mean itch increase 0.1 (SD 2.0)) rather than a decrease (mean itch decrease 0.9 (SD 1.2)) in electrical itch evoked after histamine (suggesting disturbed CIM), and more selective attention towards negative words (mean reaction time itch–neutral words 2.2 s (SD 7.1) vs. 1.2 s (SD 2.1), respectively). However, levels of itch evoked by the monofilaments (mean 0.6 (SD 1.2) vs. mean 1.0 (SD 0.6), respectively) and the electrical stimulation (mean 3.8 (SD 2.9) vs. 4.2 (SD 3.0), respectively) were slightly lower in the patients with post-traumatic stress and they showed less selective attention towards itch words (M reaction time itch–neutral words 0.7 s (SD 5.5) vs. 1.8 s (SD 2.8), respectively) than the patients without post-traumatic stress.

DISCUSSION

This study is the first to explore psychophysiological processes underlying chronic itch in patients recovered from burn injury. There were tendencies towards significance only for higher levels of itch induced by certain itch stimuli in the patients compared with the healthy subjects. In addition, the patients did not display an impaired CIM by either an itching or painful conditioning stimulus, nor did they display a heightened selective attention towards itch stimuli. Given the exploratory nature of this study, and consequently limited statistical power, future research should confirm these preliminary findings in larger samples of patients. Nevertheless, the study provides first indications that processes other than those that are assumed to play a role in chronic pain and, more recently, have also been related to chronic itch due to inflammatory dermatoses, such as atopic dermatitis, might underlie chronic post-burn itch.

The patients were generally severely affected by the burn scars, as reflected by the relatively high total body surface area burnt, and a relatively large proportion of subjects had post-traumatic stress (20). The patients' burn-related quality of life was comparable to norm groups of long-term post-burn patients (e.g. 21).

There were tendencies towards significance only for higher levels of itch due to the mechanical and histamine itch stimuli in the patients with chronic itch due to burn injury compared with the healthy subjects, which may be indicative for heightened sensitivity to itch. However, from the present results it cannot be concluded that supraspinal central sensitization of itch (5, 6) plays a role in patients with chronic itch due to burn wounds. The majority of patients had burn injuries in dermatomes ipsilaterally or contralaterally to the application location of the itch stimuli, although these had been applied to unaffected skin. Over 85% of the patients reported the itch to be located only or mainly in the areas affected by the burn scars, which is not indicative for sensitization on a supraspinal level. A possible explanation of the chronic itch in these patients could be that chronic post-burn itch results from continuing or intermittent peripheral somatosensory input from the burn scars, for which presence of central sensitization cannot be excluded.

The finding that the patients with chronic post-burn itch generally did not show impaired CIM contrasts to the large body of evidence showing that CPM efficacy is impaired in patients with chronic pain, and findings that impaired CPM is prognostic for developing long-term pain (e.g. 7, 22). Moreover, the finding that itch seems to be effectively modulated by CPT seems contrary to previous findings that the modulatory effect of a painful conditioning stimulus is restricted to painful test stimuli (23). In addition, our finding that itch seems to be effectively modulated by histamine contrasts with preliminary evidence indicating that CIM is impaired in chronic psoriatic itch (14). Although further research is required, results indicate that persistent itch after burn injury seems not to result from an impaired modulation.

The fact that the patients with post-burn itch did not display heightened selective attention towards itch-related stimuli is contradictory to what might have been expected based on studies of chronic pain (8, 9) and a study showing that patients recovered from burns, who do not necessarily have chronic itch, displayed selective attention towards burn-related words (15). However, our preliminary results should be interpreted with caution. Previous studies in the field of pain using a similar task (for pain) showed mixed results, which was also related to the type of words used (8). The words in the present study, varying from itching to nettle and head lice, might not have been of specific relevance for patients with burn-related itch. Moreover, attentional processing of itch-words might also differ from attentional processing of perceived itch.

Of the above-mentioned psychophysiological processes, only the tendencies for higher levels of itch in the patients than in the controls induced by some of the stimuli may be indicative for possible involvement of similar psychophysiological processes that have previously been linked to chronic pain and chronic itch (5–14). These findings may be related to the fact that itch in burn injury is due to localized trauma instead of affecting multiple and continuously varying body parts, such as in inflammatory dermatoses.

This study has some limitations. First, considering the exploratory character of the study, the number of included patients and controls, and thereby the power (increased risk of type-II error), was limited. Therefore, the results are only first indications, which should be replicated in future studies and investigated more in-depth in a larger sample of patients. Moreover, future research should also further elucidate the role of post-traumatic stress in chronic itch in these patients. Secondly, all reports of the severity of burn injury are based on self-report. A more detailed assessment of the localization of the burn injury, e.g. by clinical measures of physicians, might be more reliable to distinguish between peripheral and central processes. Clinical data could contribute to exactly map the areas of burn injury. Thirdly, whereas histamine might not play a major role in chronic post-burn itch (1), future research should also include itch induction methods that are non-histaminergic, e.g. cowhage (24). In addition, as generalization of experimentally induced itch to chronic spontaneous itch is not straightforward, future studies should also be directed to investigate ways to psychophysiological processes of spontaneous itch. Fourthly, as the CIM paradigm has only sparsely been used and a substantial proportion of the healthy subjects did not experience mechanically induced itch, these findings should be interpreted with extra caution.

To conclude, the trends that patients with chronic post-burn itch might be more sensitive to certain itch stimuli, and the lack of significant differences between patients and controls on conditioned itch modulation or selective attention towards itch stimuli do not indicate a major role of central sensitization. Considering that patients mainly report itch to be localized in the burn scars, spontaneous itch might be strongly based on peripheral input, for which sensitization processes cannot be excluded. This would also have implications for the treatment of post-burn itch. It needs to be further elucidated whether treatments focusing on short-term alleviation of itch might be effective for these patients; for example, by medical treatments that temporarily alleviate itch (25), and by psychological therapies, such as distraction or relaxation exercises, which might be effective in post-burn itch (26).

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