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## Pruritus and Burn Wounds

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# Pruritus and Burn Wounds

## Guest Editor

Robert S. Kirsner, MD

**Completion Time:** The estimated time to completion for this activity is 1 hour.

**Target Audience:** This CME activity is intended for dermatologists, surgeons, internists, and physicians who treat burn wounds.

### At the conclusion of this activity, the participant should be able to:

- 1) Recognize the problem of itching or pruritus in the healed burn wound
- 2) Discuss the current theories as to pathogenesis of pruritus
- 3) Recognize the current treatment modalities used for pruritus, including success rate and failure
- 4) Discuss the basis for the new modalities being pursued for itching.

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**Abstract:** Survivors of burn injury often experience severe pruritus that affects their quality of life post discharge. Antihistamines and moisturizing lotions are the mainstay of therapy for post-burn itch, but these agents provide effective relief of itch for only a minority of survivors. With the increase in patient survival now achieved by improvements in care, and the prevalence of less severe burns, the need to improve the quality of life of burn survivors through better control of wound itch has become a defined goal for care givers. Here we discuss therapeutic modalities tested for relief of post-burn itch, including the novel agent, topical doxepin cream. Results demonstrating that topical doxepin cream is superior to oral antihistamines and skin moisturizers appear to identify it as an alternative to standard of care for severe pruritus after burn injury.

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## Introduction

The problem of itch for the burn survivor and the need for a more effective treatment were first noted formally in 1988. At that time, Gordon wrote, "Burn-related pruritus is a serious problem that often receives little attention, even though it continues to aggravate burn patients during their post-burn course of treatment and rehabilitation."<sup>1</sup> Bell, et al., added, "No succinctly defined method of treatment (for pruritus in burns) is found in the literature."<sup>2</sup> This situation was addressed again in two Delphi studies designed to set priorities for burn nursing research. Marvin, et al., cited "identification of modalities most effective in controlling post-burn itching" as the third-ranked research priority, after issues related to pain control,<sup>3</sup> and Bayley, et al., reported, "What modalities are effective in controlling post-burn itching?" and "Are some of these more

effective than others?" as the top ranking questions according to impact on patient welfare.<sup>4</sup> The recent statements by O'Connell that, "Itching in the healing burn patient is reported as one of the most problematic and distressing post-burn issues that the patient experiences," and that, "The staff in any burn center can attest to the fact that no single agent or combination of agents is entirely effective in combating the patient's itch,"<sup>5</sup> remind us once more that itch remains a quality-of-life issue for the burn survivor and that an effective treatment for post-burn itch remains to be found.

## Characteristics of Post-Burn Itch

The itch experienced by the burn survivor has been described by three criteria: incidence, severity, and duration. Early anecdotal comments identify post-burn itch as a common<sup>6</sup> or universal<sup>7</sup> problem, although later numerical estimates indicate that the incidence of this symptom lies somewhere between 16 and 87 percent for adults<sup>8,9</sup> and between 57 and 100 percent for children.<sup>10,11</sup> Reports of itch severity, described using a 10-point linear visual analog scale, average 4.5 to 7.6 for all patients,<sup>9,12</sup> itch described in terms of its impact on quality of life has been noted to interfere with sleeping, eating, working, leisure or play, and therapy routines.<sup>2,13,14</sup> The severity of itch is inversely related to scar development,<sup>11</sup> worse for partial-thickness burns, most pronounced at night,<sup>2</sup> and triggered and enhanced by heat.<sup>15</sup> Itch is cited to begin as the epidermal layer heals over the wound,<sup>16</sup> to become a problem if the time for closure is more than three weeks,<sup>9</sup> and to continue for months<sup>17</sup> to years after discharge.<sup>18</sup>

## Relationship of Itch to Pain

Itch and pain have been considered sensations induced by mild or severe stimuli mediated by a common neural pathway. Clinical observations indicate that itch and pain are separate sensory modalities: They can be experienced simultaneously at the same location; the reflex response to itch is to scratch, while that to pain is withdrawal; morphine elicits itch but suppresses pain; and pain, but usually not itch, is provoked by deeper stimuli in the skin.<sup>19</sup> Experimental observations supporting this separation include the discovery of individual C-fibers in the cutaneous branch of the human peroneal nerve that are selectively sensitive to excitation by histamine,<sup>20</sup> and the related demonstration that this selectivity extends to more central spinothalamic tract neurons in the cat.<sup>21</sup> How other agents associated with itch (serotonin, prostaglandins, platelet-activating

factor, kallikrein, cytokines, proteases, tachykinins, opioid peptides, and acetylcholine)<sup>21,22</sup> fit into this paradigm remains to be determined. These agents could influence itch by increasing the release of histamine, potentiating the response to histamine, or inducing itch directly through their respective receptors.

## Novel Approaches to Treatment

In the absence of a preventative measure, treatment of post-burn itch is initiated when itching begins. Early intervention is important for the sake of patient comfort as well as to prevent scratching, which can lead to excoriation of the wound and delayed wound healing. Topical corticosteroids are not used on newly healed burns due to the risk of thinning of the skin and infection. Treatments currently applied routinely to relieve itch include moisturizing or lubricating ointments to control xerosis, pressure garments to decrease blood flow and histamine release, and oral antihistamines to compete with histamine for H<sub>1</sub> receptors. The use of antihistamine therapy to treat post-burn itch has been based on experimental evidence that histamine is pruritogenic<sup>24</sup> and clinical evidence that histamine is responsible for the itch-associated pruritic conditions, i.e., urticaria.<sup>25</sup> Supplementary treatments include cool baths or compresses and distraction and relaxation techniques. Reviews of reports describing four experimental treatments for post-burn itch provide evidence of their respective efficacies.

**Antihistamines.** Vitale, et al., conducted a prospective trial of the efficacy of three oral antihistamines:<sup>9</sup> diphenhydramine (Benadryl<sup>®</sup>, Parke-Davis, div. of Warner-Lambert, Morris Plains, New Jersey), hydroxyzine (Atarax<sup>®</sup>, Roerig Division of Pfizer, New York, New York), and the combination of phenylephrine, phenylpropanolamine, pyrilamine, and chlorpheniramine (Polyhist Forte<sup>®</sup>, Mikart, Atlanta, Georgia).<sup>9</sup> All patients were adults with a mean age of  $35.9 \pm 12.8$  years and a mean burn size of  $19.1 \pm 15.3$  percent of total body surface area. The mean severity of itch was  $7.6 \pm 1.9$  using a 10-point visual linear analog scale. Patients were started on one of the three agents, and the agents were changed monthly in a random fashion. Efficacy was determined by onset of action, duration of action, and level of relief obtained for each agent. Complete relief was defined as a drop to 0 on the itch scale, and partial relief was defined as a drop of one level or greater but not to zero.

The onset of action was similar for the three agents, ranging from 34 to 43 minutes. The duration of action was shortest for Benadryl ( $2.7 \pm 1.0$  hours), intermediate for Atarax ( $4.4 \pm 1.7$  hours), and longest for Polyhist Forte ( $6.1 \pm 2.8$  hours). Itching was completely relieved in 40 percent of patients receiving

Atarax and 10 percent of patients receiving Benadryl or Polihist Forte. Partial or no relief of itching occurred for 90 percent of patients receiving Benadryl, 60 percent of patients receiving Atarax, and 90 percent of patients receiving Polihist Forte, representing significant failure rates for all of these agents. Half of the patients experiencing a poor response to one agent benefited from changing to another agent, with the best result from Benadryl to Atarax. About one-third of the patients responding to each drug developed a tolerance, but the response was restored for most by an increase in dose.

Baker, et al., has more recently compared the efficacy of a combination of cetirizine and cimetidine or Benadryl with two topical lotions containing aloe vera for relief of burn wound itch.<sup>12</sup> Cetirizine, a selective H<sub>1</sub> receptor antagonist (Zyrtec®, Pfizer, New York, New York), and cimetidine, a selective H<sub>2</sub> receptor antagonist (Tagamet®, GlaxoSmithKline, Pittsburgh, Pennsylvania), were combined for this study based on the demonstrated benefit of these agents in chronic urticaria.<sup>27</sup> Seventeen patients completed the present study; their mean age was 35.7 years (range 10–60 years), and their total body surface area involvement ranged from 10 to 50 percent. Following the Graeco-Latin square design, the combinations of medications were changed every fourth day over a total 16-day period. Given that no significant results were obtained for the topical lotions, controlling for oral medications, and evidence that treatments over the three latter time periods were confounded by the influence of residual levels of previous medications, we describe only the effects found for Zyrtec/Tagamet versus Benadryl for the initial four-day period.

Prior to medication, the total mean itch scores for the Zyrtec/Tagamet and Benadryl groups were 4.4 and 5, respectively. At one-hour post medication, these values decreased significantly to 3.2 and 4, respectively; at six hours, these values reached their nadir at 2.7 and 4.7; and at 12 hours, these values rose to 3.1 and 5.4, respectively. The greater antipruritic effect and duration of action found for Zyrtec/Tagamet in this study may suggest a benefit of antagonism of H<sub>2</sub> receptors on skin blood vessels, although this remains speculative without a test of Zyrtec alone versus Benadryl.

**Bathing products.** Matheson, et al., tested two shower and bath oils to relieve post-burn itch in a search for a drug-free alternative to augment the maximal allowable daily dose of antihistamine.<sup>28</sup> The products chosen for testing included one containing liquid paraffin with five-percent colloidal oatmeal and another containing liquid paraffin only. Thirty-four burn patients aged 14 to 64 years with partial-thickness wounds began their participation between days 5 and 7 post burn and continued their participation for 12 ± 4 days. Bathing subjects had test product added to their bath water, and showering sub-

jects had an assistant apply the product after showering. The products were rinsed off, wound dressings were reapplied, and moisturizer was rubbed into closed wounds. Summary outcome variables were itch rating on a linear five-point scale and antihistamine (methdilazine) usage.

Patients using the liquid paraffin with colloidal oatmeal reported a mean daily itch of 0.8 ± 0.1, and those using the liquid paraffin alone reported a mean daily itch of 1.7 ± 0.1. Antihistamine usage by the former group averaged 3.1 ± 0.8mg, and usage by the latter group averaged 7.8 ± 1mg. These results indicate that the severity of itch and antihistamine usage by patients were reduced by half during the time of the use of the bath product with colloidal oatmeal. The authors suggest that the early use of these products may influence the fibroplasia characterizing partial-thickness wounds about one week after injury but offer no mechanistic explanation of their results and no definition of the components of oatmeal that may have produced these results.

**Local anesthetics.** Kopecky, et al., has considered the use of EMLA to reduce post-burn itch based upon the role of C-fibers in the itch sensation and the possible contribution of peripheral nerve regeneration to this symptom.<sup>29</sup> EMLA® (Astra Zeneca, Wilmington, Delaware) denotes a eutectic mixture of local anesthetics composed of a 1:1 mixture of lidocaine and prilocaine, which has been approved for anesthetic use in a wide variety of painful procedures involving newly formed or intact skin.<sup>30</sup> This study involved five children with a mean age of 3 ± 1.6 years and deemed not to be sensitive to chemicals and drugs causing methemoglobinemia. The study period was three days—two days to collect control data (number of itch episodes, frequency of administered antihistamine, and itch intensity scores) and one day of treatment with EMLA. EMLA (2gm/10cm<sup>2</sup>) was applied once to a single itchy site of a maximum area dictated by the patient's weight, and the site was occluded with a sterile adhesive dressing. Patients were monitored for clinical signs of hypoxia, and blood specimens were taken to quantitate methemoglobin levels.

The mean number of pruritic episodes on pretreatment Day 1 (0.8 ± 0.5) and Day 2 (1.0 ± 0.7) were significantly greater compared to Day 3 (no pruritic episodes), and the mean number of antihistamine breakthrough doses administered on Day 1 (1.2 ± 0.8) and Day 2 (1.2 ± 1.1) were significantly greater compared to Day 3 (no doses given). Lower visual analog scores observed after anesthetic application were not statistically significant, likely due to the low initial visual analog scale values and the small size of the study population. The authors conclude that EMLA seems to be a safe, novel treatment for post-burn pruritus in burned children when applied to newly healed, intact skin. However, it should be noted that methemoglobinemia

has been reported with the use of components of EMLA, so when widespread areas are treated, caution must be exercised.

**Unna boot.** Barone, et al., has evaluated the use of a gauze bandage impregnated with glycerin, zinc oxide, and calamine lotion for treatment of lower-extremity burn wounds excoriated by pruritus in pediatric patients.<sup>14</sup> This need for the Unna boot in this situation is based on experience that pediatric patients, unable to control their scratching, can excoriate itchy wounds to allow secondary infection and promote additional scarring and even chronic wound development. When standard care for pruritus is ineffective, more concrete measures may be required. Historical applications of the Unna boot for the treatment of venous stasis ulcers<sup>31</sup> and evidence that it allows for early ambulation and shortened hospital stay when used for grafted, lower-extremity wounds<sup>32</sup> also support its use in this situation.

The study population included six male patients with an average age of five years (range 17–120 months) who had sustained lower-extremity burns with an average total body surface area of 11 percent. All underwent excision and split-thickness skin grafting. On evaluation one week after discharge, all patients had excoriation of their grafts involving an average 2cm x 5cm. The patients were randomly divided into two groups to be treated with either an Unna boot (with all antihistamines discontinued) or a conventional dressing (i.e., Xeroflo, bacitracin, and gauze) and Atarax alternated with Benadryl. The Unna boot was changed every seven days as an outpatient procedure, and the conventional dressing was changed daily by the parents. The average time for complete wound closure and appearance of the healed wounds was comparable for the two groups. However, questioning the parents involved revealed statistically improved appetites, sleep, and play patterns in the children treated with the Unna boot. Additional benefits of the Unna boot over the conventional dressing were the lower time (15 min/wk vs. 3.5 hr/wk) and treatment cost (\$19.80/wk vs. \$30.90/wk) involved.

**Massage.** Field, et al., has taken still another approach to addressing the problem of post-burn itch.<sup>12</sup> This approach has been based on evidence that massage therapy reduces various types of pain, including pain associated with debridement.<sup>34</sup> Twenty patients with an average age of 38 years were recruited to participate in this study during the healing phase of wound healing, 80 to 165 days post injury. Participants were randomly assigned to massage therapy or standard medical care. Standard medical care included application of cocoa butter, without massage, to closed wounds; massage therapy involved 30-minute sessions twice a week for five weeks, using cocoa butter as a lubricant. Itch scores on a 10-point scale were reduced from 5.8 to 1.7 after the first session and from 2.8 to 0.8

after the last session. Comparable scores for the control group were 5.8 to 4.9 and 6.9 to 5.6, respectively. These results demonstrate a clear benefit of massage therapy for post-burn itch, though the mechanism of this phenomenon remains to be identified.

**Tricyclic antidepressant.** Doxepin, a tricyclic antidepressant, has recently been tested for the relief of post-burn itch by Demling and DeSanti.<sup>35</sup> It has been found to have potent H<sub>1</sub> and H<sub>2</sub> receptor blocking properties, being approximately 50 times more potent than hydroxyzine and nearly 800 times more potent than diphenhydramine.<sup>36</sup> A five-percent topical cream has been found to inhibit the pruritus induced experimentally by histamine,<sup>37</sup> as well as relieve the pruritus associated with atopic dermatitis,<sup>38</sup> eczema,<sup>39</sup> and urticaria.<sup>40</sup> Serum levels of doxepin applied topically are usually not measurable but, when detected, are over 25 times lower than the serum level required to produce any therapeutic central nervous system activity.<sup>41</sup> These conditions support testing of topical doxepin cream for the treatment of burn wound pruritus that is not adequately controlled by standard treatment modalities.

Twenty patients selected for study were adults (ages 18 to 55 years) with pruritic middermal, nonexcised, nongrafted wounds covering 10 to 40 percent of body surface area; their pruritic wound sites involved an average nine percent of body surface area (range 6% to 13%), had required an average 19 days to heal (range 15 to 25 days), and had been totally reepithelialized for at least two months in order to avoid confusing the pain of open areas with itching. All patients were being managed in an outpatient setting using a standard care regimen: oral antihistamines, sedatives, and skin moisturizers. Ten patients used pressure garments. All patients had pruritus in portions of their wounds for at least two weeks sufficient to impair their quality of life through effects on physical activity, sleep, and overall comfort, despite this care. Patients were supplied with a tube containing five-percent doxepin cream (Prudoxin®, Healthpoint, Fort Worth, Texas) sufficient to apply to itching wounds as a thin layer, three to four times a day, for a seven-day period. Oral antihistamines, sedatives, and skin moisturizers were stopped for the trial period; pressure garments were allowed for the patients currently using them.

On baseline Day 1, average itch score was 7 (range 5 to 8) on a 10-point scale. Immediately after beginning doxepin use on the first study day, all patients described a significant decrease in itching, represented by an average itch score of  $3 \pm 1$ , and this level of relief continued throughout the seven-day study period, indicating the absence of tolerance. Itch scores returned to the pre-doxepin level two days after discontinuation of treatment and return of standard care. Erythema scores followed a similar pattern of reduction and recovery. Thus, there was no

evidence of a rebound increase in histamine release other than of the pre-doxepin level. The only complication or side effect reported was somnolence, which was reported by four subjects who noted it to be limited to the first day or two of the trial and comparable to that resulting from standard care oral antihistamine use.

These trial results demonstrate that topical doxepin significantly decreases post-burn itching as soon as it is applied and that the control of itching continues as long as the cream is being applied. There was no correlation between the degree of somnolence and relief from itching, indicating that the antipruritic influence of doxepin reflected its local actions. A placebo effect cannot be ruled out, but it is noteworthy that this population is quite skeptical of beneficial effects given their experience with a variety of antihistamines and moisturizers. Also against a placebo effect were the decreases in both itching and erythema for all patients involved.

It is not possible to know the mechanism of action of doxepin in this application, but there is much room to speculate. The potent ability of tricyclic compounds to antagonize H<sub>1</sub> and H<sub>2</sub> receptors identifies one action likely to contribute to the antipruritic effect of doxepin, although H<sub>2</sub> receptors are involved in itch. Other possible pharmacologic mechanisms for this effect of doxepin include antagonism of  $\alpha$ -adrenergic, muscarinic, and serotonin receptors 5-HT<sub>2</sub> subtype; inhibition of norepinephrine and serotonin neuronal reuptake; inhibition of platelet-activating factor production; and local anesthetic activity.<sup>36,42-46</sup>

## Summary

Current standard measures of controlling post-burn itch do not provide reliable and effective relief of this symptom for the majority of burn survivors, allowing itch to become a quality-of-life issue for these individuals.<sup>1-5</sup> The absence of methods to prevent or control post-burn itch can be attributed to the effort given to reducing mortality from thermal injury<sup>47</sup> and a lack of knowledge about anatomical and physiological aspects of itch on which to base laboratory or clinical testing. However, with growing knowledge of agents capable of producing or influencing the itch response,<sup>22</sup> itch signaling,<sup>20</sup> cutaneous neuroanatomy,<sup>48</sup> and cell sources of histamine,<sup>49</sup> new opportunity is available to identify and test novel therapeutic agents for treatment of post-burn itch.

Experimental therapies for post-burn itch reviewed in this report represent a range of modalities including oral antihistamines, bathing products, local anesthetics (EMLA), Unna boot, massage, and a tricyclic antidepressant in topical cream form.

All of these treatments have reduced post-burn itch, although results reported indicate that itch is seldom completely abolished by therapy. Further, these results also demonstrate that itch will return when therapy is discontinued. Therefore, the goal of preventing itch, or permanently interrupting the pathway(s) and positive feedback cycle(s) responsible for chronic itch, remains to be achieved. However, it is clear that several therapeutic alternatives are available to suppress post-burn itch to a tolerable level and that therapies directed at the affected sites may be more effective than oral agents for improving the survivor's quality of life through suppression of itch. Further, given the possibility that pruritogenic agents in addition to histamine may contribute to post-burn itch, it becomes important to consider the utility agents with broad activities, i.e., doxepin, for this application.

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### Questions (Select one answer per question)

1. Itching in the post burn wound is:
  - A. Most prominent in the burn healing in less than 7 days
  - B. Is worse for the grafted full-thickness burn
  - C. Is often triggered by heat
  - D. Typically has a short course, i.e. days in the deep partial thickness burn
2. Mediators reported to be involved with itch include all but:
  - A. Histamine
  - B. Serotonin
  - C. Prostaglandins
  - D. Tumor necrosis factor
3. The most common anti-mediator therapy for post-burn itch is:
  - A. Antihistamines
  - B. Antiprostanoids
  - C. Corticosteroids
  - D. Antioxidants
4. Partial or no relief from itching with the use of oral diphenhydramine was reported in the following percent of patients:
  - A. 80-90%
  - B. 40-50%
  - C. 20-30%
  - D. 10%
5. Doxepin is an agent with all of the following properties except:
  - A. Tricyclic agent
  - B. Potent antihistamine
  - C. Effective against urticaria
  - D. Produces bradycardia
6. Doxepin in a 5% cream has been found to be effective for:
  - A. Depression
  - B. Itching in atopic dermatitis and urticaria
  - C. Psoriasis
  - D. Wound healing
7. Other techniques used to control itching include all of the following except:
  - A. Massage therapy
  - B. Pressure garments
  - C. Moisturizers
  - D. Hot baths
8. Which cutaneous nerve fibers appear responsible for itching:
  - A. A fibers
  - B. B fibers
  - C. C fibers
  - D. D fibers
9. In the study of post burn itch and Doxepin cream results indicated:
  - A. A significant decrease in itch
  - B. No change in itch
  - C. An increase in erythema
  - D. A 100% incidence of somnolence
10. The following agents have antihistamine properties except:
  - A. Doxepin
  - B. Hydroxyzine
  - C. Propranolol
  - D. Chlorphenhydramine

**Pruritus and Burn Wounds Answer and Evaluation Form**

Please print clearly:

Name	Degree	Position/Title	
Organization/Institute	Department		
Mailing Address for Certificate (H or W):			
City	State	Zip Code	Email Address
Social Security Number	Phone (area code)	Fax (area code)	

**Answers** (Refer to questions on other side of page) Circle one letter for each answer:

- |                |                |
|----------------|----------------|
| 1.     A B C D | 6.     A B C D |
| 2.     A B C D | 7.     A B C D |
| 3.     A B C D | 8.     A B C D |
| 4.     A B C D | 9.     A B C D |
| 5.     A B C D | 10.    A B C D |

**Evaluation (circle one)**

Excellent (4) Good (3) Satisfactory (2) Poor (1)

Accuracy and timeliness of content:	4	3	2	1
Relevance to your daily practice:	4	3	2	1
Impact on your professional effectiveness:	4	3	2	1
Relevance of the content to the learning objectives:	4	3	2	1
Effectiveness of the teaching/learning methods:	4	3	2	1
This activity avoided commercial bias or influence	YES	NO		

**Now that you have read this article, can you:**

- |  |     |    |
|--|-----|----|
| 1) Recognize the problem of itching or pruritus in the healed burn wound?                            | YES | NO |
| 2) Discuss the current theories as to pathogenesis of pruritus?                                      | YES | NO |
| 3) Recognize the current treatment modalities used for pruritus, including success rate and failure? | YES | NO |
| 4) Discuss the basis for the new modalities being pursued for itching?                               | YES | NO |

What questions do you still have? \_\_\_\_\_

How will you use what you have learned from this activity? \_\_\_\_\_

All tests must be received by 2/1/03.