# Treatment of pruritus with topically applied opiate receptor antagonist

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***Background:*** Pruritus is the most common and distressing skin symptom, and treatment of itch is a problem for thousands of people. The currently available therapies are not very effective. Therefore there is an urgent need to find new effective topical drugs against itching.

***Objective:*** We conducted two separate studies to evaluate the efficacy of topically applied naltrexone, an opioid receptor antagonist, in the treatment of severe pruritus. The objective of the first open study was to correlate the clinical efficacy of topically applied naltrexone in different pruritic skin disorders to a change of epidermal $\mu$-opiate receptor (MOR) expression. The second study was a double-blind, placebo-controlled, crossover study on pruritus in atopic dermatitis.

***Methods:*** Initially we performed an open pilot study on 18 patients with different chronic pruritic disorders using a topical formulation of 1% naltrexone for 2 weeks. A punch biopsy was performed in 11 patients before and after the application of the naltrexone cream and the staining of epidermal MOR was measured. Subsequently, a randomized, placebo-controlled, crossover trial was performed with the same formulation. We included in this trial 40 patients with localized and generalized atopic dermatitis with severe pruritus.

***Results:*** In the open study more than 70% of the patients using the 1% naltrexone cream experienced a significant reduction of pruritus. More interestingly, the topical treatment with naltrexone caused an increase of epidermal MOR staining. The regulation of the epidermal opioid receptor correlated with the clinical assessment. The placebo-controlled, crossover trial demonstrated clearly that the cream containing naltrexone had an overall 29.4% better effect compared with placebo. The formulation containing naltrexone required a median of 46 minutes to reduce the itch symptoms to 50%; the placebo, 74 minutes.

***Limitations:*** We could only take biopsy specimens in 11 patients, which means that a satisfactory statistical analysis of the changes of epidermal MOR staining was not possible. In addition, there was an insufficient number of patients with nephrogenic pruritus and pruritic psoriasis to draw definitive conclusions.

***Conclusions:*** The placebo-controlled study showed a significant advantage of topically applied naltrexone over the placebo formulation. This finding is supported by the biopsy results from the open studies, showing a regulation of MOR expression in epidermis after treatment with topical naltrexone, especially in atopic dermatitis. These results clearly show potential for topically applied opioid receptor antagonist in the treatment of pruritus. The placebo formulation also had some antipruritic effects. This underlines the importance of rehydration therapy for dry skin in the treatment of pruritus. (J Am Acad Dermatol 2007;56:979-88.)

Pruritus or itch is defined as an unpleasant subjective sensation associated with the desire to scratch. Pruritus induces a mechanical defense reaction, including pressing, rubbing, or scratching. The scratching leads to new irritation of the skin and this in turn induces pruritus, which

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*Abbreviations used:*

CNS: central nervous system
FAS: full analysis set
MOR: $\mu$-opioid receptor
PP: per protocol
SPID: sum of the pruritus intensity difference
VAS: visual analogue scale

creates a vicious circle.[1] Pruritus is the most common and distressing skin symptom. The treatment of itch is a problem for thousands of people and is important not only for dermatology but also for all other medical specialties. The currently available topically applied drugs for pruritus, such as the antihistamines or polidocanol, are restricted by their limited efficacy when used by this route of administration and by their ability to sensitize. In addition, most patients with chronic pruritus do not respond to systemic treatment with antihistamines or steroids. Therefore there is an urgent need to find new effective drugs against itching.

For many years it has been suggested that the itch sensation is related to pain, and, indeed, the opioid peptides can influence the pain and itch sensation in a reversed way. Pruritus is a well-known and hard-to-control side effect of treatment with opioids for pain relief.[2] On the other hand, opioid-receptor antagonists, such as naltrexone and naloxone, have been used to treat different forms of chronic pruritus.[3-5] There have been several double-blind, placebo-controlled studies proving the effect of systemically applied naltrexone and naloxone in hepatogenic pruritus.[6-8] In addition, plasma from patients who have pruritus associated with chronic cholestasis induced opioid receptor–mediated scratching in monkeys,[9] and naltrexone treatment of this pruritus in humans precipitated an opioid withdrawal-like reaction.[10] These observations suggest a crucial role of the opioid receptor system and its ligands, such as $\beta$-endorphin, in chronic cholestatic pruritus. Systemically applied naltrexone reduced itching not only in patients with hepatogenic pruritus, but also in those with different pruritic skin diseases, such as atopic dermatitis, xerosis cutis, cutaneous lymphoma, and prurigo nodularis.[4] However, systemic naltrexone seemed to have no significant effect against uremic pruritus in a double-blind, placebo-controlled study.[11]

There is still an ongoing discussion as to whether this elicitation of itch is due to opioid receptors in the central nervous system (CNS) or in the peripheral nervous system. One of the most important indications that the opioid-induced pruritus is at least partially elicited in the periphery comes from the double-blind controlled studies with the opioid receptor antagonist methylnaltrexone. Methylnaltrexone, a novel quaternary derivative of naltrexone that does not cross the blood-brain barrier, acts as a selective peripheral opioid receptor antagonist and decreases pruritus and constipation, but still has an adequate maintenance of pain control.[2,12] This indicates that pruritus is elicited in the peripheral nervous system and modified in the CNS. Therefore we wanted to study the effect of a topically applied opioid-receptor antagonist against different forms of pruritus.

## METHODS

### Study objectives and design

**Open pilot study.** The main objective of this study was to see whether the topical application of the opioid-receptor antagonist naltrexone has an antipruritic effect and whether there is an objective effect, as studied by immunohistology. Therefore in two study centers we treated 18 patients with different pruritic disorders with a cream containing 1% naltrexone to see which kind of pruritus responds better to this treatment. The patients had to apply the study cream at the itching locations at least twice a day. The general intensity of the pruritus was measured by using a visual analogue scale (VAS) from 1 to 100 mm and the patients had to record the intensity of pruritus in their diaries in the morning, at noon, and in the evening. In addition, after 8 and 15 days the patient had to assess, together with the physician, the overall changes of pruritus. The clinical efficacy was judged according to the changes of the scratching intensity in the VAS as noted in the diary compared with day 0 (start of study). Additionally, in 11 patients we carried out a punch biopsy at the site of intense itching before and after the local treatment with the opioid receptor antagonist. The epidermal expression of $\mu$-opiate receptor (MOR) and the changes of epidermal nerve endings were observed and semiquantified by immunohistochemistry using confocal microscopy. This pilot study showed that the topically applied opioid receptor antagonist worked best on patients with chronic pruritus associated with atopic dermatitis and lichen simplex chronicus.

**Placebo-controlled, crossover study.** We planned a second multicenter, randomized, double-blind, placebo-controlled, crossover, phase II study on patients with atopic dermatitis. The goal of this study was to confirm in a double-blind study design that topically applied naltrexone indeed has an antipruritic effect in atopic dermatitis. The study took 4 to 6 weeks and included 40 patients with severe attacks of pruritus. The patients were required to visit the study center 4 times:

- Visit 1: 14 days, wash-in phase
- Visit 2: Day 0, randomization of the patient and start of therapy with one cream
- Visit 3: control of patient's diary and change of cream; day 7 or 14, depending on whether the patient had had 3 severe bouts of scratching in 1 or 2 weeks
- Visit 4: collection of creams, control of diary, final questionnaire and end of study; day 14, 21, or 28

The diary was not only used to record the itch sensation during the bouts of itching, but also to record the location of the pruritic attacks, the use of rescue medication, and side effects. The patients had to go through a wash-in phase of 2 weeks, where they could apply the normal basic treatment of the atopic dermatitis with their own rehydrating cream and, if necessary, the previous therapies such as systemic antihistamines. During these 2 weeks the patients had to record 3 bouts of itching (>50 mm VAS). The intensity of the pruritus was recorded in a patient diary at the following times: 0 hours (start of study), 20 minutes, 40 minutes, 1 hour, 2 hours, 3 hours, and 4 hours. Overall, only a few pruritus attacks were not documented completely over 4 hours. However, in those cases, missing values were imputed by the last available documentation (also called "last value carried forward" principle). This is a conservative method commonly used in placebo-controlled trials.

The patients were randomized and they entered the study with the placebo or the naltrexone-cream in a double-blind study design. The basic treatment of the dry skin was continued unchanged during the entire duration of the study. The patient had again to record 3 severe bouts of itching during 1 or 2 weeks in the patient diary. If the patient experienced severe pruritus, he or she applied the study cream topically and recorded the itch sensation on a VAS at the time points mentioned above. The patient had to experience, treat, and record at least 3 severe bouts of itching (VAS >50 mm) in 2 weeks. After 1 to 2 weeks the study cream was changed in a crossover study design and the patient had again to record and treat 3 severe bouts of itching in 1-2 weeks. The patients were allowed to use the study cream freely during the study, also against other attacks of pruritus.

### Selection of study participants

For the open study, patients were chosen who had a severe chronic pruritus of different origin. All of these patients previously had several different unsuccessful treatments. The diagnoses of the different patients can be seen in Table I. Patients younger than 18 years and pregnant woman were excluded. This study was performed in Switzerland (Basel and Schaffhausen).

The second, double-blind study included patients older than 18 years with atopic dermatitis. They were recruited in 3 different study centers in Germany. The bouts of pruritus had to be more than 50 mm in a VAS from 0 to 100 mm, which represents a pruritus of strong intensity. Exclusion criteria were infectious skin diseases, known allergies against the ingredients of the drugs, acute eczema, malignant diseases, drug abuse, severe neurological or psychological diseases, and pregnancy. Two weeks before and during the study, the patients were not allowed to use the following drugs: systemic opioids and their antagonists, systemic steroids and antibiotics, topical tacrolimus or pimecrolimus. As rescue medication, topical steroids were allowed to be used, but the patient had to record this, and the use of topical steroids was not allowed during the time of measurements of itching intensity.

### Immunostaining and semiquantification of epidermal PGP 9.5 and MOR staining (open study)

With informed consent, 3-mm punch biopsy specimens were taken from pruritic skin just before local treatment with naltrexone. Two weeks after regular application of naltrexone cream, another 3-mm punch biopsy specimen was taken from the same area (~1 cm away from the first biopsy). The biopsy specimens were fixed for at least 12 hours in 4% formaldehyde and embedded in paraffin. The paraffin-embedded skin biopsy sections were cut, dried overnight at 37°C, and deparaffinized. The primary antibody used for immunofluorescence was a polyclonal rabbit anti–$\mu$-opioid receptor antibody (Diasorin). A cyanine dye (Cy2)–conjugated goat anti-rabbit IgG for MOR was used as a secondary antibody. Confocal microscopy was performed with a Zeiss Confocal Laser Scanning Microscope LSM 510, inverted Axiovert 100 M (Carl Zeiss AG, Jena, Germany). It operates in the sequential acquisition mode to exclude cross talk between channels. The 488 excitation line was used and the optics used was a Zeiss Plan-Neofluar 40× oil immersion objective with a numerical aperture of 1.3. Optical sections, 0.9 $\mu$m thickness, were scanned through the z-plane of the sample. The amount of fluorescent staining in epidermis was semiquantified by using the Imaris statistic software package.

### Efficacy and safety evaluations

Swiss ethical committees approved the open pilot study in 2001 (E 407/01). The double-blind study was approved by German (number 03182 of the

**Table I.** Correlation of clinical efficacy of naltrexone cream to epidermal MOR expression (immunofluorescence) in the open pilot study

| Patient No. | Age (y) | Skin disease | Clinical efficacy | Change of MOR expression | Location of biopsy |
|---|---|---|---|---|---|
| 01 | 74 | AD | − | − | Finger |
| 02 | 79 | Prurigo simplex | ++ | + | Back |
| 03 | 22 | AD | + | + | Upper arm |
| 05 | 46 | LSC | ++ | + | Lower leg |
| 07 | 38 | Nephrogenic pruritus | − | = | Elbow |
| 08 | 61 | Prurigo simplex | + | + | Upper arm |
| 09 | 46 | AD | ++ | = | Upper arm |
| 11 | 20 | AD | + | ++ | Upper arm |
| 12 | 40 | AD | ++ | + | Upper arm |
| 13 | 46 | Psoriasis inverse | ++ | ++ | Shoulder |
| 14 | 63 | Nephrogenic pruritus | + | − | Upper arm |

*AD*, Atopic dermatitis; *LSC*, lichen simplex chronicus; *MOR*, $\mu$-opioid receptor.

"Bayerische Landesärztekammer") and Swiss (E 248/03) ethical committees in 2003. Systemic naltrexone has been used for many years in daily concentrations between 50 and 100 mg against opioid overdoses, alcohol dependence, and, as already mentioned, against different kinds of pruritus. The safety profile and the side effects of systemic naltrexone are well known, and this knowledge can be applied to the topical applications of naltrexone. In-vitro assessment (human skin mounted in Franz diffusion cells, exposure to the test preparation for 6 hours) resulted in an epidermal naltrexone concentration of 3.3 $\mu g/cm^2$, corresponding to 6.5% of the applied dose.

The compositions of the study creams were as follows:

- Placebo cream: based on Excipial Cream, Spirig AG, Egerkingen, Switzerland (purified water, paraffin, myristyl alcohol, cetyl alcohol, glyceryl monostearate, polysorbate 20, citric acid, methyl- and propyl parabene, hexamidine diisetionate)
- Naltrexone cream: 1% naltrexone in aforementioned Excipial Cream

### Statistical analysis

For the histologic data from the open pilot study, logarithmic and square transformations were used to stabilize the variance of the semiquantitative measurements of epidermal MOR staining. The data are divided into two categories: before and after treatment. The clinical efficacy is coded by two categories: efficient = +, no effects = 0. The sample size is relatively small; therefore we chose a mixed linear model (Laird and Ware, 1982; Pinheiro and Bates, 2000) to explore the difference between the efficacy and the time (before/after treatment). This type of model considers the individual variability of each subject, and each subject was considered as a random draw in the large population.

The double-blind, placebo-controlled crossover study was subjected to rigorous statistical analysis. The efficacy data were based either on the Full Analysis Set (FAS-collective) or the Per Protocol population (PP). The patients using a "rescue medication," such as topical steroids, during the first 20 minutes were excluded from the PP analysis. Therefore the PP population includes only the patients who finished the study without relevant deviation from the protocol. The analysis of the safety data included all randomized patients who were treated at least once with the study medication (safety evaluation set). Results were considered to be statistically significant when the test revealed a $P$ value of .05 or less.

Forty-five patients were enrolled into the placebo-controlled study, and all patients were treated (safety evaluation set), but 5 patients had a relevant violation of the study protocol and were therefore excluded. Three of the patients cancelled the informed consent during the study and 2 patients had fewer than 3 pruritus attacks of more than 50 mm VAS in both or one of the study periods. Finally, the FAS collective contained 40 patients and the PP population, 39 patients. One patient used a topical steroid as "rescue medication" before the end of the 4-hour observation period in several itching attacks. The PP population did not include this patient who had deviated from the study protocol. The randomized groups "placebo-naltrexone" and "naltrexone-placebo" showed no significant differences in the FAS population with regard to age ($P$ = .75), gender ($P$ = .30), weight ($P$ = .39), and height ($P$ = .18).

The duration of pruritus in the study collective varied between 3 years and 1 week (mean, 14.5 ± 29.9 weeks). Twenty-five of the 40 patients (62.5%) had pretreatment of the pruritus; the rest had not

treated the itching symptoms before entering the study. Most of the pretreatment consisted of topical steroids; only 4 patients had systemic antihistamines. The concomitant medications during the studies included mostly drugs for cardiovascular diseases (n = 7), pain relievers (n = 3), the antidepressant maprotiline (n = 1), omeprazole (n = 1), simvastatin (n = 1), bezafibrate (n = 1), and thyroxine against hyperthyreosis (n = 1). None of the patients took antihistamines during the study period and none of them had ultraviolet irradiation therapy.

The most important statistical parameter was the "*s*um of the *p*ruritus *i*ntensity *d*ifference" (SPID) that is calculated from the VAS as follows:

$$\mathrm{SPID} = \mathrm{SUM}_{\mathrm{i}=1\ \mathrm{to}\ \mathrm{n}}\,(\mathrm{VAS[i]} - \mathrm{VAS[Baseline]})$$

Where i = 1 is the first and n the last time point of puritus measurement.

The mean SPID value from 3 recordings of bouts of itching was calculated for each time point after application of study cream (time 0). The change of intensity of pruritus sensation during the first 4 hours after application of the cream was the most important parameter measured (SPID [Δmm VAS]).

In addition to the SPID, other criterion were observed. One of them was the dynamic study of the intensity of the pruritic attacks during time in absolute values (mm VAS) and not relative to baseline. Another measurement concerned the rate of responders (defined as improvement of 10% compared with placebo) and the time needed until a 50% reduction of the itch sensation occurred.

## RESULTS

### Pilot study

The analysis of the patients' diaries revealed the following: Most of the patients recorded relief of pruritus in the first 15 minutes after application of the naltrexone cream. Most of the time the effect lasted for at least 4 hours. Most of the patients with atopic dermatitis, lichen simplex chronicus, and prurigo simplex, as well as the patient with pruritic psoriasis inversa experienced good to excellent clinical reduction of pruritus. Biopsy sections were taken before and 2 weeks after initiation of the treatment in 11 of the 18 patients. The biopsy specimen was taken at the start of the open study (time 0) from the location with the most severe sensation of pruritus. Another punch biopsy specimen was taken from the same location 2 weeks after regular application of naltrexone cream. The epidermal expression of MOR was semiquantified by immunohistochemistry and confocal microscopy. Table I summarizes the clinical and histologic results of the open pilot study.

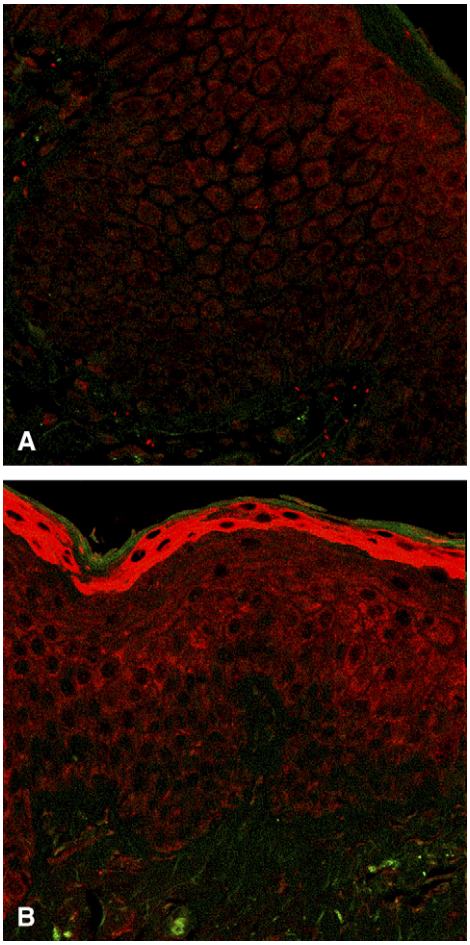


**Fig 1.** Typical down-regulation of epidermal MOR expression in a patient (patient 03) with atopic dermatitis (**A**). Up-regulation of epidermal MOR expression in this patient at the same place 2 weeks after regular topical application of 1% naltrexone in the open study (**B**).

Figs 1, *A* and 2, *A* show the typical reduction of epidermal MOR staining in chronic pruritic skin disorders, such as atopic dermatitis or lichen simplex chronicus, compared with findings from skin biopsy specimens of normal individuals without pruritus (see also Bigliardi et al[13] and Bigliardi-Qi et al[14]). However, 2 weeks after regular treatment with topically applied opioid-receptor antagonist, the epidermal MOR staining is greatly increased. This increased staining for MOR was most pronounced in the granular layer in atopic dermatitis (Fig 1, *B*). However, in lichen simplex chronicus (Fig 2, *B*) and prurigo simplex (data not shown), the up-regulation of MOR was observed in all layers of epidermis. One patient with atopic dermatitis experienced no clinical improvement of the pruritus with naltrexone. This patient had an acute dyshidrotic flare of atopic hand eczema; all other patients with atopic dermatitis experiencing good clinical efficacy had chronic

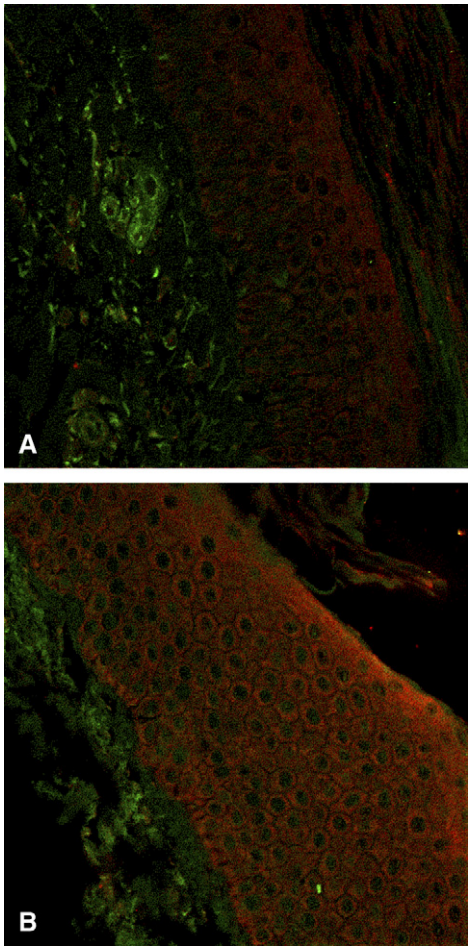


**Fig 2.** Typical down-regulation of epidermal MOR expression in a patient (patient 05) with lichen simplex chronicus (**A**). Up-regulation of epidermal MOR expression in this patient at the same place 2 weeks after regular topical application of 1% naltrexone in the open study (**B**).

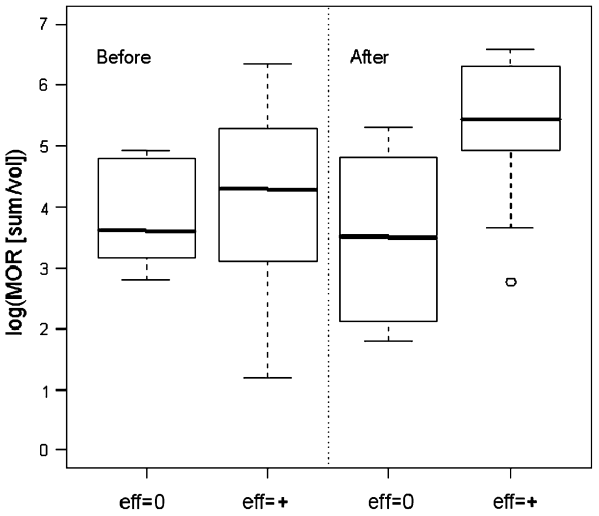


**Fig 3.** Boxplot representations of MOR (with logarithmic transformation) in relation to efficacy (eff = 0 [no clinical improvement of pruritus]/eff = + [with clinical improvement of pruritus]) and time (before/after treatment with topical naltrexone) in the open study.

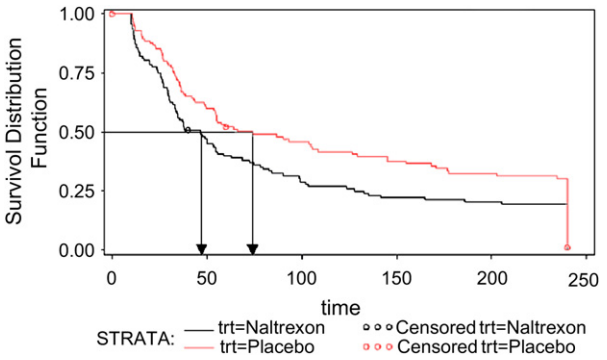


**Fig 4.** Time course of score measuring 50% reduction of pruritus in VAS (FAS population, n = 40). The Wilcoxon test revealed statistically significant difference between placebo- and naltrexone-cream ($P$ = .0073); randomized, placebo-controlled, crossover trial.

atopic dermatitis. In this particular patient there was no change of the epidermal MOR staining, and this correlated with the missing clinical effect. In addition, patients with nephrogenic pruritus did not report clinical improvement of the pruritus and the epidermal MOR expression did not change either. Fig 3 shows the boxplot representation of the epidermal MOR expression after logarithmic transformation and statistical analysis of the data. The patients without clinical efficacy [eff = 0] (1 atopic dermatitis, 1 nephrogenic pruritus) did not have a change of epidermal MOR expression. However, in the 9 patients with clinical improvement of the pruritus [eff = +] there was an increase of epidermal MOR staining. However, the number of patients was insufficient to develop a statistical model to calculate the $P$ values. The topical treatment was especially successful in patients with chronic atopic dermatitis. Therefore we decided to design a double-blind, placebo-controlled study with patients who had atopic dermatitis.

## Double-blind, placebo-controlled, crossover study

The SPID analysis shows an advantage of the naltrexone cream over the placebo cream of −51.6 mm VAS in the FAS population (−190 mm vs −243.3 mm). The placebo cream itself has an antipruritic effect if compared with the wash-in phase. However, the overall effects and the time until the antipruritic effect was obtained were different. The time was calculated until the patients felt a 50% reduction of the pruritus compared with the value at time 0. Thus the 50% reduction in pruritus intensity occurred after

**Table II.** Statistical analysis of the sum of the pruritus intensity difference values* (mm VAS) of the full analysis set and per-protocol population in total and with or without pretreatment of the pruritus: A randomized, placebo-controlled, crossover trial

| Parameter | No. of patients | Different treatments (Δ mm VAS) | Global H test (Hotelling)* | *t* Test to residual effect* | *t* Test to treatment effect* |
|---|---|---|---|---|---|
| SPID: Total | | | | | |
| FAS | 40 | P = −190.7; N = −242.3; Δ = 52.6 (**26.7%**) | .1125 | .7294 | .0347 |
| PP | 39 | P = −192.8; N = −249.6; Δ = 56.8 (**29.4%**) | .0708 | .8035 | .0206 |
| SPID: Without pretreatment | | | | | |
| FAS | 15 | P = −200.0; N = −216.4; Δ = 16.4 (**8.2%**) | .7929 | .8008 | .5292 |
| PP | 15 | P = −205.1; N = −219.3; Δ = 14.2 (**6.9%**) | .8428 | .8751 | .5713 |
| SPID: With pretreatment | | | | | |
| FAS | 25 | P = −185.2; N = −257.9; Δ = 72.7 (**39.3%**) | .0859 | .3741 | .0328 |
| PP | 24 | P = −185.1; N = −268.7; Δ = 83.4 (**45.1%**) | .0594 | .5186 | .0165 |

*FAS*, Full analysis set; *N*, naltrexone; *P*, placebo; *PP*, per protocol [population]; *SPID*, sum of the pruritus intensity difference; *VAS*, visual analogue scale.
*Data given are *P* values.

74 minutes with the placebo cream and after 46 minutes with the naltrexone cream (Fig 4). This means that the patients felt a 50% reduction of pruritus 28 minutes earlier compared with those using placebo. Fifty percent reduction of VAS after 1 hour occurred with the naltrexone formulation in 60.2% (placebo = 47.9%) and after 4 hours in 80.6% (placebo = 69.7%). The numbers of documented pruritus attacks were as follows: n = 112 for the naltrexone-formulation and n = 115 for the placebo. The Wilcoxon test revealed a significantly faster relief of pruritus with naltrexone cream compared with the placebo ($P$ = .0073). The arrows in Fig 4 depict the median. Statistical analysis of the effects of naltrexone cream versus placebo using the Student *t* test show a significant amelioration of pruritus in the naltrexone group at 20 minutes ($P$ = .0370), 40 minutes ($P$ = .0382), 1 hour ($P$ = .0281), and 2 hours ($P$ = .0404), but no longer at 3 hours ($P$ = .0775) or 4 hours ($P$ = .1664) after application of the study creams. Thus naltrexone in the present formulation has its major effect on pruritus in the first 2 hours after application. The difference between placebo and naltrexone is particularly pronounced 20 minutes after application of the cream. The Δmm VAS value at 20 minutes was −15.6 mm for placebo and −23.5 mm for naltrexone. Therefore naltrexone has a 50.6% advantage over placebo at 20 minutes, indicating that the effect of the topically applied opioid-receptor antagonist naltrexone is very fast. In addition, the statistical analysis has shown that there is no residual effect. This means that there is no significant difference if the patient used placebo or naltrexone cream first in the crossover study.

Surprisingly, there is an important difference in efficacy of topically applied naltrexone if the location of itch and application is investigated. Application of the naltrexone cream on the trunk shows no overall difference of antipruritic effects compared with placebo (changes in VAS after 2 hours: naltrexone = −34.1; placebo = −35.1). However, using the location "arms and legs," an important advantage of naltrexone over the placebo cream could be observed (changes in VAS after 2 hours: naltrexone = −55.9; placebo = −39.4).

Overall, naltrexone cream had a considerable advantage over the placebo cream during the 4-hour observation period after the pruritic attack. Topically applied naltrexone has an advantage of 26.7% in the FAS dataset and 29.4% in the PP population over the placebo cream with respect to the SPID measurement. The PP population includes all the patients who finished the study without relevant deviation from the protocol. The global H-test (Hotelling) and the *t* test for the effect of treatment show a somewhat significant advantage of the topically applied naltrexone over placebo. The treatment effect was significantly superior in the naltrexone group (Table II).

Fifteen patients had no pretreatment of the pruritus before entering the study. Observations from clinical and basic research suggest, however, that there is a difference between chronic and acute pruritus in pathogenesis and treatment.[14] Therefore we analyzed the subpopulation of patients without pretreatment and compared them with the patients with pretreatment of pruritus. We can hypothesize that the patients without pretreatment of the severe

pruritus had an acute form of pruritus, whereas patients with pretreatment had a chronic form. This analysis revealed surprising results (Table II). The patients without pretreatment had no advantage from the topical treatment with naltrexone (8.2% FAS; 6.9 PP). However, in the patients with pretreatment of the pruritus there was a significant amelioration of the pruritus by topical application of naltrexone (39.3% FAS, 45.1% PPl treatment effect, $P = .0165$). The median duration of pruritus before entering the study was 4 weeks in the population without pretreatment and 7.5 weeks in the population with pretreatment. This means that, in general, the patients with pretreatment had had the pruritus much longer than patients without pretreatment.

## DISCUSSION

On the basis of our previous observations, that the MOR system is regulated in chronic atopic dermatitis,[14] and on the basis of several clinical studies using the opioid-receptor antagonist naltrexone systemically to treat chronic itch, we decided to put naltrexone into a cream formulation at a concentration of 1% and to study the effect of topically applied opioid-receptor antagonist on chronic pruritus.

The first open prospective pilot study included patients with a pruritic skin disease not responding to traditional treatment with antihistamines or topical steroids. More than 70% of these patients with severe pruritus experienced a significant reduction of itching after 15 to 30 minutes and the effect held for 2 to 6 hours. The patients with chronic itch sensation due to atopic dermatitis, lichen simplex chronicus, and prurigo simplex responded better to this treatment than those with nephrogenic pruritus. The subjective clinical results could be backed up by an objectively measurable up-regulation of epidermal MOR staining in the stratum granulosum and stratum spinosum. The MOR expression increased in patients with good clinical response after topical treatment with the opioid-receptor antagonist naltrexone, but not in patients with no efficacy of the naltrexone. In the two patients with nephrogenic pruritus, one reported no effect with topical naltrexone and the other only a slight effect. The expression of epidermal MOR did not increase in either patient. The number of patients with nephrogenic pruritus is limited in this study. However, Peer et al[11] reported no significant amelioration of severe resistant pruritus in 15 patients receiving hemodialysis in a randomized, double-blind, placebo-controlled, crossover trial using systemic naltrexone. These data could agree with our observations, but further studies are needed to confirm the limited efficacy of naltrexone in nephrogenic pruritus.

After these very encouraging results we designed a double-blind, placebo-controlled, crossover study using patients with pruritus in atopic dermatitis. This study demonstrated clearly that the formulation containing naloxone compared with placebo had an overall 29.4% better effect, and that relief of itch symptoms was significantly faster. The naltrexone cream reduced itch symptoms to 50% in a median of 46 minutes compared with 74 minutes for the placebo formulation.

The statistical analysis showed that topical application of naltrexone had much less effect if the site of pruritus was the trunk rather than the extremities. What could explain these differences? First, the density of intraepidermal nerve fibers in a healthy subject shows a rostral-to-caudal decrease, with a linear relationship to the distance from the spine.[15-17] This effect is not age related. The changes of intraepidermal nerve fibers could explain why skin on the trunk responds less to naltrexone treatment than skin of the extremities. However, the difference could be also explained by differences of application. It is much easier to apply a cream on the extremities than on the back.

The placebo-controlled study shows that there is a significant difference between the efficacy of naltrexone cream and placebo cream, especially if only the patients whose severe pruritus was pretreated are considered. These patients had pruritus for an average of 7.5 weeks before initiation of the study; this pruritus, which had a longer pretreatment duration, could be considered chronic. The results showed significant effects of the topical application of naltrexone in patients with long-lasting pruritus (45% alleviation of pruritus by VAS measurement compared with placebo, n = 24), but not in patients with pruritus that had lasted for a shorter time and without pretreatment (7%, n = 15). This finding agrees with previous data, which have shown that the down-regulation of MOR expression is especially pronounced in chronic pruritic skin disorders with a long-lasting history of pruritus.[14]

We have previously demonstrated that human epidermal keratinocytes, fibroblasts, and melanocytes express MOR at both the mRNA and protein levels.[13] The studies of Kauser et al[18,19] and Stander et al,[20] which showed an expression of MOR in epidermal and follicular keratinocytes, in sebaceous glands and melanocytes, have confirmed this finding. Several research groups could demonstrate that MOR is not only expressed in keratinocytes but also on unmyelinated peripheral nerve fibers in the dermis and epidermis.[20,21] Three-dimensional confocal microscopy revealed that in patients with chronic atopic dermatitis the nerve endings are

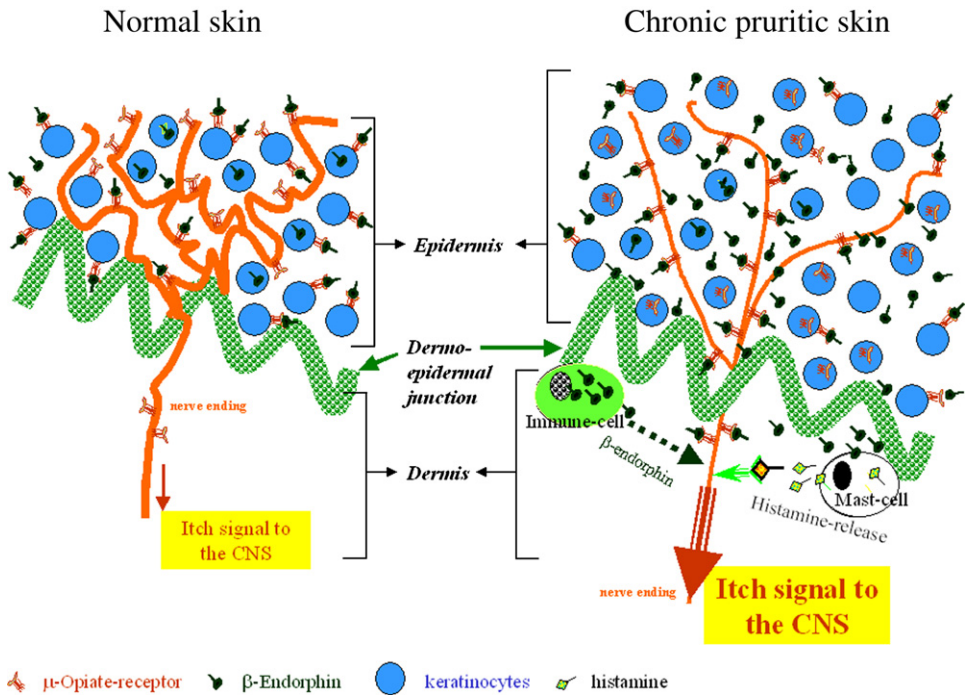


**Fig 5.** Interaction between opioid receptor on keratinocytes and nerve endings and relationship to itch signal. In normal skin, keratinocytes express high amounts of MOR; therefore endogenous ligands are bound primarily to opioid receptors on keratinocytes, competing with binding of opioid ligands on opioid receptors located on nerve endings. This results in a weak itch signal to the central nervous system (CNS). In chronic pruritic skin disorders, most opioid receptors on keratinocytes are internalized; therefore there are many opioid ligands available to bind to opioid receptors on sensory nerve endings. This leads, together with the changed morphology of the epidermal nerve endings, to a strong itch signal to the CNS.

much thinner and run straight through the epidermis.[14] In normal skin the nerve endings are rather thick and wind through the epidermis; there is also substantial branching. These morphologic changes could explain the changed sensitivity of nerve endings in chronic pruritic skin disorders. The sensory innervation in epidermis not only changes in chronic pruritic skin diseases but also in an animal model for neuropathic pain.[22] In addition, the epidermal expression of MOR was significantly reduced in patients with different chronic pruritic skin diseases.[14,23] In particular, the hypertrophic epidermis of patients with chronic atopic dermatitis shows almost no epidermal expression of MOR.[14] This down-regulation could also be observed on the mRNA level.[14] However, in this same study, no down-regulation of MOR was observed in acute contact dermatitis. The down-regulation of MOR on keratinocytes in chronic pruritic skin diseases could cause the following effects: (1) The endogenous ligands for the MOR system are no longer bound to the MOR on keratinocytes and therefore more ligands are available to bind to the MOR on epidermal nerve endings. This could result in an increase of the itch signal to the CNS. (2) The epidermal nerve fibers are stretched in the hypertrophic epidermis, and this increases the sensitivity of the peripheral nerve endings, resulting again in an increased itch signal. The up-regulation of the epidermal MOR expression in most of the chronic pruritic disorders after treatment with topical naltrexone could reduce pruritus by binding the free opioid ligands to the epidermal keratinocytes. This makes fewer opioid ligands available for binding to the epidermal nerve endings. In addition, naltrexone could have a direct effect on the opioid receptor signaling in peripheral nerve endings. All these effects lead to a decrease of pruritus, as we have observed in the open and placebo-controlled study described in this paper. Fig 5 summarizes the hypothesis of interactions between the opioid receptor system on keratinocytes and nerve endings and its relationship to pruritus.

Overall, the naltrexone formulation shows clear advantages over placebo as an antipruritic drug. However, in the double-blind, placebo-controlled study on patients with atopic dermatitis, the placebo also showed some antipruritic effects. This again

proves the well-known antipruritic potential of a basic water-in-oil formulation. Dry skin plays a crucial part in the pathogenesis of most pruritic disorders. A recent publication by Palmer et al[24] stresses the important role of the epidermal barrier formation in atopic dermatitis. This epidermal barrier is severely disturbed by a loss-function-mutation in the filaggrin gene in most of the patients with atopic dermatitis.[24,25] The dry skin induces cracks, and this exposes the epidermal nerve endings directly to the air. An ointment prevents the direct exposure of free nerve endings to air and irritants by occlusion. This could result in an immediate reduction of pruritus. There are still many open questions about the pathophysiological role of opioid receptors in skin and the interaction between keratinocytes and free nerve endings in pruritus. However, these two studies establish the clinical relevance of the MOR system and the peripheral epidermal nerve endings in chronic pruritus. Further basic and clinical research is warranted to open the way to new therapeutic approaches for this burdensome symptom, pruritus.

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