

Primary care

Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study

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Abstract

Objective To explore the efficacy and safety of fluticasone propionate, cream and ointment, applied twice weekly in addition to maintenance treatment with emollients, in reducing the risk of relapse of chronic recurrent atopic dermatitis.

Design Randomised, double blind, parallel group study of 20 weeks' duration.

Setting Dermatology outpatient clinics (6 countries, 39 centres).

Participants Adult (aged 12-65) patients with moderate to severe atopic dermatitis who were experiencing a flare.

Methods Participants applied fluticasone propionate (0.05% cream or 0.005% ointment; once or twice daily) regularly for four weeks to stabilise their condition. The patients whose disease was brought under control then continued into a 16 week maintenance phase, applying emollient on a daily basis with a bath oil as needed and either the same formulation of fluticasone propionate or its placebo base (emollient alone) twice weekly to the areas that were usually affected.

Main outcome measure Time to relapse of atopic dermatitis during maintenance phase.

Results 376 patients entered the stabilisation phase, and 295 continued into the maintenance phase. After 16 weeks in the maintenance phase, the disease remained under control in 133 patients (87 using fluticasone propionate twice weekly, 46 using emollient alone), 135 (40 fluticasone propionate, 95 emollient) had experienced a relapse, and 27 had discontinued. Median time to relapse was six weeks for emollient alone compared with more than 16 weeks for additional fluticasone propionate. Patients who applied fluticasone propionate cream twice weekly were 5.8 times less likely (95% confidence interval 3.1 to 10.8, $P < 0.001$) and patients using fluticasone propionate ointment 1.9 times less likely (1.2 to 3.2, $P = 0.010$) to have a relapse than patients applying emollient alone. The groups showed no differences in adverse events.

Conclusion After atopic dermatitis had been stabilised the addition of fluticasone propionate twice

weekly to maintenance treatment with emollients significantly reduced the risk of relapse.

Introduction

Currently no standard management plan exists for the long term treatment of moderate to severe atopic dermatitis.¹ A recent comprehensive systematic review found that most practitioners use one of two approaches: either a potent topical corticosteroid followed by a lower potency preparation as the condition improves or a short course of topical corticosteroid followed by a maintenance regimen of emollients.¹ Concerns have been expressed about the prolonged use of low potency topical corticosteroids, and, although treatment with emollient is safe, its efficacy as a maintenance treatment is limited.²⁻⁴ Moreover, there is little evidence to support either of the practices.^{1,5} Others have suggested a maintenance treatment of emollient combined with intermittent topical corticosteroid.² This approach was investigated recently in a small scale study, which showed that remission of atopic dermatitis can be maintained with daily emollient plus fluticasone propionate applied twice weekly to areas of the skin that had healed but were prone to relapse.⁴

In the United Kingdom both the ointment and the cream formulations of fluticasone propionate are classified as potent topical corticosteroids.⁶ Fluticasone propionate is one of the newer type of topical corticosteroids and has high topical anti-inflammatory effects and a low potential to cause adverse effects because of low systemic absorption and rapid metabolism and clearance.⁷⁻¹¹ This profile of benefits and risks is advantageous in a long term treatment strategy. This trial aimed to evaluate further the use of fluticasone propionate twice weekly as part of an emollient based maintenance regimen in patients with moderate to severe atopic dermatitis.

Patients and methods

Study design

This was a randomised, double blind, placebo controlled, parallel group, European study. The primary objective was to evaluate the efficacy and safety of the

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addition of fluticasone propionate twice weekly to an emollient maintenance regimen in reducing the risk of relapse of atopic dermatitis.

Patients

Patients (age 12-65 years) with recurrent moderate to severe atopic dermatitis were eligible for the study and were recruited during a flare of atopic dermatitis (see assessments for definition).¹² This was assessed from an index lesion (a typical lesion on the patient's neck, hands, or flexural sites of the elbows or knees). We excluded patients with any medical condition for which topical corticosteroids were contraindicated, those with other dermatological conditions that may have prevented accurate assessment of atopic dermatitis, and those receiving any concomitant medications that might have affected the study's outcome. Patients provided written informed consent.

Treatments

Initially the flare was stabilised with fluticasone propionate cream 0.05% or fluticasone propionate ointment 0.005%, once or twice daily, for four weeks. Patients who achieved remission (see assessments) then entered a maintenance phase and, using the same formulation as in the stabilisation phase, applied fluticasone propionate or its placebo base on two successive evenings per week for up to 16 weeks. They applied treatment to all healed sites of potential relapse and any newly occurring sites. In addition, patients in both treatment groups routinely applied emollient (cetomacrogol based cream) twice daily (once on treatment days) and used a bath oil as needed. Patients in the group randomised to twice weekly placebo base were therefore essentially receiving emollient alone as maintenance treatment.

Assessments

Atopic dermatitis was assessed by using the three item severity (TIS) score (the sum of three signs: erythema, oedema or papulations, and excoriations; each scored 0=absent, 1=mild, 2=moderate, or 3=severe).¹³ The

score shows good correlation with objective SCORAD, a well validated scoring system for atopic dermatitis.¹³ We defined a flare or relapse as a score of 4 or higher. At the start of the study, for recruitment purposes, an index lesion was assessed, but during the maintenance phase a flare occurring at any site was to be assessed. We defined remission or control as an index lesion score of 1 or lower (absent or mild). Patients were assessed every two weeks in the stabilisation phase and after two, six, 10, and 16 weeks in the maintenance phase. At each visit patients were questioned about adverse events, and the investigator recorded these. In addition patients had regular examinations for visual evidence of skin atrophy.

Analysis

The randomisation code determined the treatment that each patient received through the stabilisation and maintenance phase. Investigators at each centre allocated patients to treatment groups in equal numbers according to a computer generated randomisation code. The block size for the study was eight, and each recruiting centre received 16 treatment allocation numbers.

The primary end point was the time to relapse of atopic dermatitis during the maintenance phase. Based on data from a previous study, to detect a treatment difference at the 5% two sided significance level with 90% power (log rank test), we estimated that 58 patients were required per treatment group in the stabilisation phase.^{5 14} In addition we estimated that at least 55% of patients in the stabilisation phase would be eligible for maintenance treatment; therefore at least 110 patients per treatment arm were required.

We conducted all analyses on an intention to treat basis (all subjects were included in the analysis if they were randomised and applied the study medication at least once). Confirmatory analyses conducted on per protocol populations (all patients who fulfilled all the major protocol criteria) proved unnecessary as fewer

Table 1 Baseline demographics at study entry (start of stabilisation phase). Values are numbers (%) of patients unless otherwise indicated

	Fluticasone propionate cream		Fluticasone propionate ointment		Total
	Once daily	Twice daily	Once daily	Twice daily	
No of patients	95	91	100	90	376
Mean age in years (SD)	28.4 (12.2)	28.1 (11.8)	29.6 (13.3)	28.9 (12.4)	28.8 (12.4)
Sex:					
Female	51 (54)	49 (54)	54 (54)	51 (57)	205 (55)
Male	44 (46)	42 (46)	46 (46)	39 (43)	171 (45)
Race:					
White	85 (89)	84 (92)	91 (91)	84 (93)	344 (91)
Black	7 (7)	2 (2)	4 (4)	0	13 (3)
Other	3 (3)	5 (5)	5 (5)	6 (7)	19 (5)
Duration of atopic dermatitis:					
≤5 years	17 (18)	10 (11)	14 (14)	12 (13)	53 (14)
>5 years	78 (82)	81 (89)	86 (86)	78 (87)	323 (86)
Duration of current episode:					
≤3 weeks	30 (32)	26 (29)	26 (26)	26 (29)	108 (29)
>3 weeks	65 (68)	65 (71)	74 (74)	64 (71)	268 (71)
Mean (SD) extent of atopic dermatitis (%)*:	28.8 (19.0)†	17.7 (16.2)	17.5 (14.6)†	18.4 (16.1)	18.6 (16.5)
Median three item severity score at index lesion (range) ‡	5.0 (4-6)	5.0 (4-9)	5.0 (4-7)	5.0 (4-7)	5.0 (4-9)

*Percentage of 13 body areas (front and back of head, front and back of left and right arm, chest, back, front and back of left and right leg, external genitalia).

†Data missing for one patient.

‡Sum of erythema, oedema or papulations, and excoriations (scored 0-3). The score ranges between 0 (none) and 9 (severe).

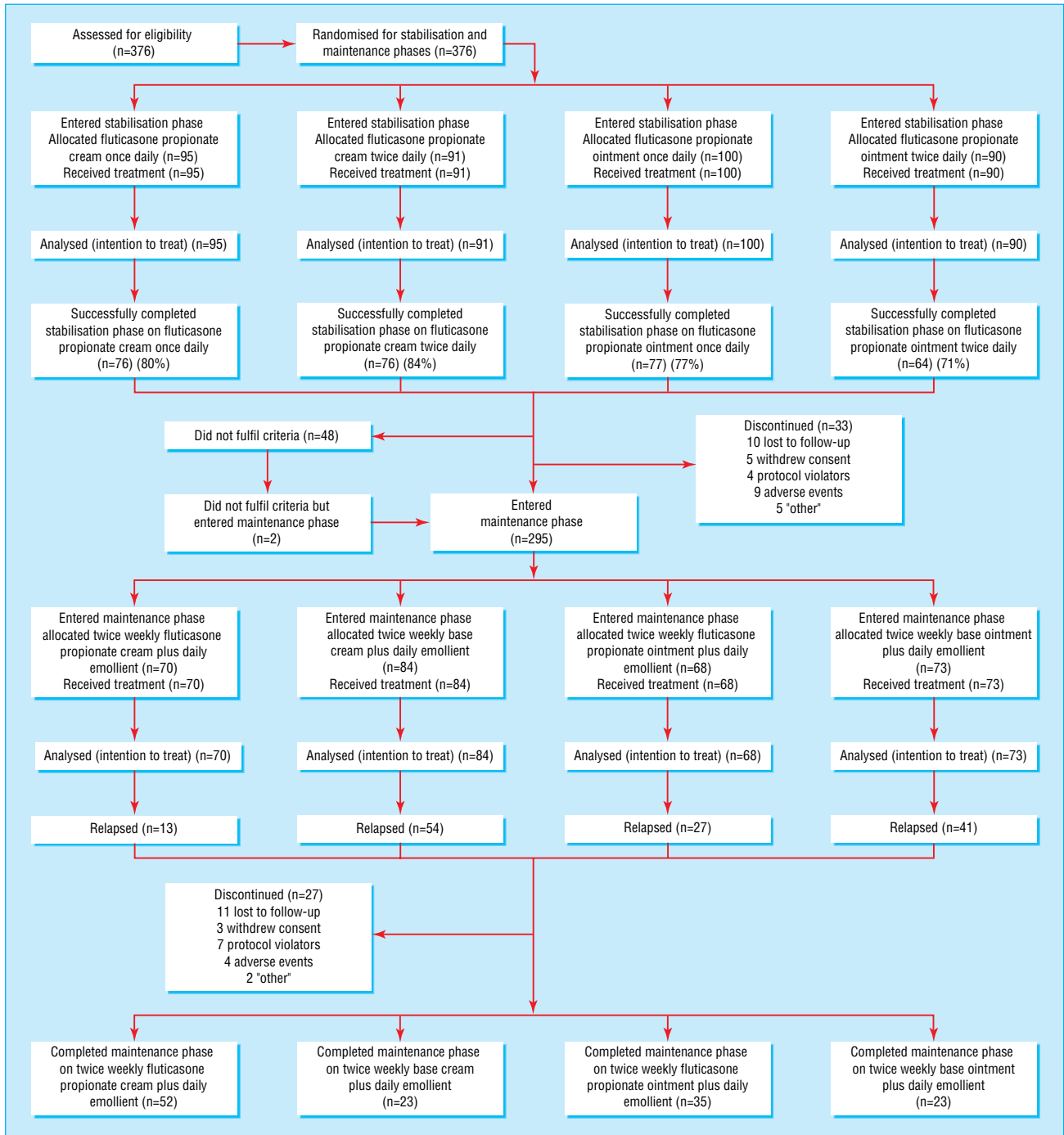


Fig 1 Flow chart of patients

than 20% of the patients in the study population violated the protocol.

We defined time to relapse of atopic dermatitis as the time from entry into the maintenance phase until a relapse occurred. We used Cox's proportional hazards regression model to compare treatment groups, using terms for country, frequency of treatment in the stabilisation phase, age, and sex.¹⁵ We used the Kaplan-Meier product limit method to estimate the distribution of time to relapse of atopic dermatitis.¹⁶ We calculated summary statistics such as median time to relapse and proportions of patients who were relapse free from the estimates. We used a Cochran-Mantel-Haenszel statis-

tic, adjusting for country, to determine the secondary end point, the proportion of patients with controlled atopic dermatitis at the end of the stabilisation phase.

Results

Accountability and demographics of patients

We recruited and screened a total of 376 patients (171 male, 205 female) from 39 centres in six countries from January 1998 to July 1999. Table 1 shows demographic details. After the condition had been stabilised by regular daily treatment with fluticasone propionate, 295 patients continued into the maintenance phase (33

Table 2 Summary of analysis of time to relapse in the maintenance phase

	Group using cream		Group using ointment	
	Daily emollient* plus twice weekly fluticasone propionate (n=70)	Daily emollient* plus twice weekly base (placebo) (n=84)	Daily emollient* plus twice weekly fluticasone propionate (n=68)	Daily emollient* plus twice weekly base (placebo) (n=73)
No (%) of patients having a relapse	13 (19)	54 (64)	27 (40)	41 (56)
% difference between placebo and fluticasone propionate (95% CI)	46 (32 to 59)		16 (0.2 to 33)	
Median time to relapse in weeks	>16	6.1	>16	6.1
Hazard ratio (base:fluticasone propionate)†	5.8 (95% CI 3.1 to 10.8, P<0.001)		1.9 (1.2 to 3.2, P=0.010)	
Number needed to treat‡	2.2		6.1	

*Twice daily (once daily on study treatment days) plus bath oil as required.

†Based on the probability of a relapse occurring at any time point in the study, on one treatment relative to the other.

‡Number of patients who have to be treated with fluticasone propionate to prevent one relapse that would have occurred on placebo.

discontinued, 48 did not meet eligibility criteria). After 16 weeks the disease remained controlled in 133 patients (87 using fluticasone propionate twice weekly, 46 emollient alone), 135 patients (40 fluticasone propionate, 95 emollient alone) had experienced a relapse, and 27 patients had discontinued (fig 1).

Table 2 shows results for the primary end point. For the cream formulation we found a significant (P<0.001) difference in time to relapse of atopic dermatitis during the maintenance phase, with a hazard ratio of 5.8 (95% confidence interval 3.1 to 10.8), indicating that patients adding fluticasone propionate cream twice weekly into their emollient maintenance regimen reduced the risk of relapse to approximately one sixth of that on emollient alone. The median time to relapse on twice weekly fluticasone propionate exceeded 16 weeks (the duration of the study), whereas on emollient alone it was 6.1 weeks (fig 2).

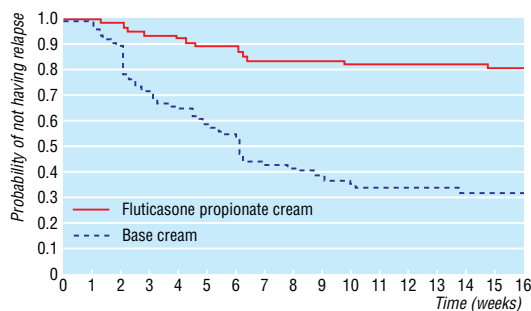


Fig 2 Kaplan-Meier plot showing the probability of remaining free from relapse during the 16 week maintenance phase. In the double blind study, twice weekly fluticasone propionate cream or its base (placebo) was used in addition to maintenance treatment with emollients

For the ointment formulation, the difference that treatment made was also significant (P=0.010), with a hazard ratio of 1.9 (1.2 to 3.2), indicating that patients adding fluticasone propionate ointment twice weekly into their emollient maintenance regimen reduced their risk of relapse to approximately half of that on emollient alone. The median times to relapse on ointment were similar to the times achieved on cream (table 2 and fig 3).

In comparison with fluticasone propionate cream twice weekly more patients applying fluticasone propionate ointment twice weekly had experienced a relapse by 16 weeks (19% versus 40%). The difference

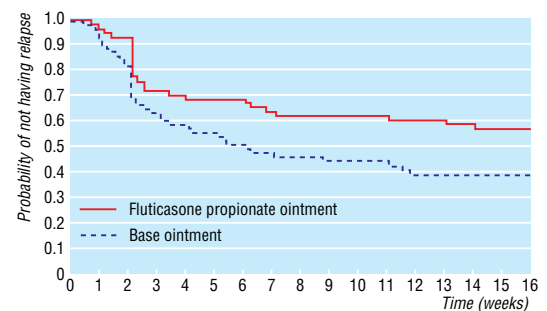


Fig 3 Kaplan-Meier plot showing the probability of remaining free from relapse during the 16 week maintenance phase. In the double blind study, fluticasone propionate ointment or its base (placebo) was used twice weekly in addition to maintenance treatment with emollients

between the two formulations was significant (P=0.002), with a hazard ratio of 2.9 (1.5 to 5.9), indicating that patients using the cream formulation were approximately one third as likely to have a relapse as those using the ointment.

For most patients relapses occurred at previously treated sites, and only seven patients experienced a relapse at a new, untreated site. Of these, six patients were in the group being treated with emollient alone and one in the group being treated with fluticasone propionate ointment twice weekly.

Data from the initial stabilisation phase showed that proportions of patients in remission at the end of this four week phase were similar across the four treatment groups (fig 1). Analysis showed no significant difference between application once and twice daily (P=0.546 for fluticasone propionate cream and P=0.249 for fluticasone propionate ointment).

Adverse events

The most common adverse event was ear, nose, and throat infection, which occurred in nine subjects during the stabilisation phase. Four adverse events were classified as serious (an episode of erysipelas, an exacerbation of asthma, and two flares of eczema). During the maintenance phase investigators made no reports of visual signs of skin changes and of atrophy. During the stabilisation phase visual signs of atrophy related to study treatment were reported in three subjects. Two of these used fluticasone propionate ointment once a day and were reported as having telangiectasia and striae, respectively, and one used fluticasone propionate cream twice a day and was reported to have telangiectasia. However, two of these

patients had a previous history of skin changes, and therefore only one report was newly observed.

Discussion

Fluticasone propionate cream or ointment, added twice weekly to maintenance treatment with emollients only, reduced the risk of relapse in patients with atopic dermatitis. This study is one of the few randomised, controlled, clinical trials to examine longer term management of moderate to severe atopic dermatitis. Rather than focusing on initial healing rates, we examined maintenance of remission and assessed the effect of treatment on the risk of relapse, an important clinical outcome in this chronic relapsing skin condition. For fluticasone propionate cream, the risk of relapse was reduced to approximately one sixth, and for fluticasone propionate ointment it was reduced to approximately half. Although the median time to relapse for patients using emollient alone was approximately six weeks (which shows the beneficial effect of routine maintenance treatment with emollient), the median time to relapse for patients adding fluticasone propionate twice weekly was substantially longer and in excess of 16 weeks (study duration). Crucial to the success of the twice weekly maintenance treatment was the initial stabilisation of an acute flare by regular daily treatment with fluticasone propionate (for up to four weeks). We found no evidence that the frequency with which fluticasone propionate was applied (once or twice daily) in the stabilisation phase affected the outcome in the maintenance phase.

All treatment regimens were equally well tolerated, with only one reported drug related visual skin change (telangiectasia during the stabilisation phase) over 20 weeks. Ultrasound and skin biopsies in previous studies, where fluticasone propionate was used either continuously (for up to nine months) or intermittently, have shown that fluticasone propionate has low atrophogenic potential.^{4 8 9} We did not assess the function of the hypothalamic-pituitary-adrenal axis in this study. However, several previous studies in both adults and children, including some as young as 3 months, in whom the surface area of the body was affected extensively, have shown that fluticasone propionate exerts no significant effect on basal or stimulated plasma concentrations of cortisol or 24 hour urinary concentrations of cortisol during short or long term treatment.^{4 7 10 11}

Both formulations of fluticasone propionate were effective, but cream was more effective than ointment. Several previous studies have shown the efficacy of fluticasone propionate cream and ointment in controlling atopic dermatitis, but this is the first to compare both formulations in one clinical trial.⁷ Although the concentrations of the two preparations differed (fluticasone propionate 0.005% weight for weight (w/w) ointment, fluticasone propionate 0.05% w/w cream), they were specifically formulated to provide appropriate amounts of local release of corticosteroid and show equivalent potency as determined by the established vasoconstrictor assay.⁶ On the basis of these data we assumed that the two formulations would display a similar efficacy. However, the potency and ranking of a topical corticosteroid preparation, based on its ability to cause skin vasoconstriction in normal healthy

What is already known on this subject

Atopic dermatitis is characterised by frequent, unpredictable relapses, and there is little evidence to support any of the commonly used practices for long term maintenance treatment of moderate to severe cases

What this study adds

After stabilisation of an acute flare, adding fluticasone propionate cream or ointment twice weekly to daily emollient treatment significantly reduced the risk of patients experiencing a further relapse and extended remission time

This regimen seemed to be well tolerated, with a low risk of local adverse effects, and may paradoxically be steroid sparing since, by producing longer remission periods, it should reduce the need for intensive treatment with topical corticosteroids as is often required to control flares

volunteers, may not totally reflect its performance in treating healed and active lesions of atopic dermatitis. In addition, although ointments are generally thought to be more effective than creams because of their occlusive properties, which enhance drug penetration, patients often find them messier to use and less cosmetically acceptable than creams.^{17 18} This may well have affected patients' compliance with the ointment; we monitored adherence to treatment by means of patients' daily diaries, but tube weights were not recorded. The unexpected difference between formulations requires further investigation.

This treatment regimen for fluticasone propionate may paradoxically be steroid sparing in patients with atopic dermatitis. It produces longer remission periods and should therefore reduce the number of acute, intensive courses of treatment with topical corticosteroids that are often required to control flares. In addition, by maintaining remission in the longer term, application of fluticasone propionate twice weekly will be limited mainly to previously healed sites, which are less permeable than inflamed lesions, and so the overall exposure to topical corticosteroids will be reduced even further. The use of the simple three item score system for monitoring the severity of atopic dermatitis will help doctors in deciding the best time to implement the twice weekly maintenance treatment. Whether or not this maintenance treatment strategy can be applied to other topical corticosteroids of lower potency remains to be established. Nevertheless, these results with fluticasone propionate represent an important step towards the successful long term management of atopic dermatitis, a condition for which effective treatment options are limited.

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