STUDY

Psychological Distress Impairs Clearance of Psoriasis in Patients Treated With Photochemotherapy

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Objective: To assess whether psychological distress affects treatment outcome in psoriasis.

Design: Cohort study of patients with psoriasis receiving psoralen–UV-A (PUVA) photochemotherapy.

Setting: Two university hospital dermatology departments.

Patients: One hundred twelve patients with chronic plaque psoriasis.

Main Outcome Measures: We assessed clinical severity of psoriasis, psychological distress, and other potential confounders of treatment outcome such as skin phototype, family history of psoriasis, and alcohol intake before starting PUVA therapy. Clinical severity of disease and response to therapy were assessed at every fourth appointment.

Results: Pathological or high-level worry was the only significant ($P=.01$) predictor of time taken for PUVA to clear psoriasis. Event curves of time to clearance significantly differed between high- and low-level worry groups (log rank test, 6.64; $df=1$; $P=.01$). Patients in the high-level worry group cleared with PUVA treatment at a rate 1.8 times slower than that of the low-level worry group (ExpB=1.81; 95% confidence interval, 1.13-2.90). Fiftieth percentile time to clearance of psoriasis in the high- and low-level worry groups showed a median difference of 19 days.

Conclusions: Psychological distress, in the form of excessive worrying, has a significant and detrimental affect on treatment outcome in patients with psoriasis. Patients with psoriasis who are classified as high-level worriers may benefit from adjunctive psychological intervention before and during treatment. These findings provide further evidence of the existence of a brain-skin axis.

Arch Dermatol. 2003;139:752-756

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ACCUMULATING EVIDENCE suggests that psychological distress can have detrimental effects on normal human physiology[1-5] and on the physiology of the skin in particular.[6,7] The long-term stress imparted from care of a demented relative can significantly impair healing of skin biopsy wounds in such caregivers.[6] Recently, Garg et al[8] demonstrated that skin barrier function is significantly impaired by stress induced by examination anxiety in students.

Inflammatory skin diseases, most notably psoriasis, are often believed by patients to be initiated or exacerbated by stressful life events. In a recent survey, 60% of a patient sample with psoriasis at our institution believed this to be the case.[9] Patients with psoriasis differ in their pattern of autonomic response to stress compared with control subjects[10] and show an increase in sensory nerves,[11] whose neuropeptide content is higher in individuals with high stress levels relative to their counterparts with low stress levels.[12] Stress appears to exacerbate psoriasis; moreover, patients with psoriasis exhibit significant psychosocial disability,[13] avoidance coping,[14] and automatic vigilance for negative cues pertaining to the reaction of others to their disease.[15]

Indirect evidence of an association between psychological stress or distress and the clinical course of psoriasis comes from the use of stress reduction techniques to improve the disease. Cognitive behavior therapy as an adjunct to regular therapy has been shown to significantly improve the clinical severity of psoriasis during the 6-week course of treatment and for at least 6 months afterward.[16] Another small study[17] found that patients who listened to a stress-reduction tape as they were undergoing psoralen–UV-A (PUVA) photochemotherapy or UV-B phototherapy for psoriasis had a significantly faster time to

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improvement of their psoriasis compared with patients receiving standard PUVA or UV-B therapy. On the basis of this evidence, we asked whether those patients with psoriasis who have high levels of psychological distress in the form of worrying are less likely to respond to treatment.

When investigating whether psychological factors can influence the effectiveness of a particular therapy for psoriasis, we must consider that noncompliance with treatment can be a confounding variable. As many as 39% of patients with psoriasis do not comply with treatment regimens.[18] To mitigate this potential confounding effect, we chose PUVA as our test therapy, because patient compliance with this mode of treatment can be accurately documented on the basis of attendance at the hospital-based phototherapy unit. The principal aim of the study, therefore, was to assess the effects of psychological factors on the time taken to achieve clearance of psoriasis in patients who were being treated with PUVA.

METHODS

STUDY POPULATION

A total of 122 patients with a dermatologist-confirmed diagnosis of chronic plaque psoriasis were entered into the study at the following 2 centers: the Dermatology Centre, Hope Hospital, Manchester, England, and the City of Dublin Skin and Cancer Hospital, Dublin, Ireland. Patients were eligible to participate if they were aged 18 to 70 years and were not receiving any systemic treatment for their psoriasis, other than PUVA, or any psychotropic medication currently or within the previous 6 months. Patients were interviewed and recruited during a 2-year period. Measurement of the clinical severity of psoriasis was performed by dermatologists (B.K. and T.M.) unaware of results of psychometric assessment of patients.

DESIGN AND PROCEDURE

Assessments

On entry into the study, patients underwent the following clinical and psychosocial assessments:

1. Clinical severity of psoriasis was assessed by means of the well-characterized Psoriasis Area and Severity Index (PASI).[19] The PASI provides an overall measure of clinical severity of psoriasis (ranging from 0-72) by combining estimates of the percentage of the area of skin involved with a score for the 3 main clinical manifestations of the condition (ie, erythema, induration, and desquamation). Participants underwent subsequent clinical assessment by means of the PASI on every fourth hospital appointment. Clearance of psoriasis was defined as less than 1% of total body surface area affected by psoriasis.
2. Skin phototype was assessed according to the Fitzpatrick criteria.[20]
3. Alcohol intake per week was assessed by means of self-report, as some evidence suggests that alcohol ingestion can affect psoriasis severity.[21]
4. Before starting PUVA therapy, participants completed the following standardized psychological assessments. Anxiety and depression were assessed by means of the Hospital Anxiety and Depression Scale.[22] This 14-item scale was developed for use in patients with medical conditions and has previously been found to be useful in dermatology patients.[23] Items are rated on a scale of 0 to 3, indicating the strength of agreement with that item. Thus, scores for each subscale range from 0 to 21. Pathological worrying was assessed by means of the Penn State Worry Questionnaire (PSWQ).[24] This 16-item scale has been shown to be a valid and reliable measure of pathological worry in this population.[25] Items such as "I find it easy to dismiss worrisome thoughts" or "my worries overwhelm me" are rated on a scale of 1 to 5 (1 indicates "not at all typical of me"; 5, "very typical of me"). The PSWQ has high internal consistency ($\alpha > .90$)[26] and a good test-retest reliability and discriminant validity.[24] Although worry is a relatively normal phenomenon and may relate to attempts at problem solving, evidence suggests that pathological worrying may be qualitatively different from normal worry.[27] Thus, the published cutoff scores of 60 and greater than 60 for the PSWQ, where greater than 60 indicates pathological worry, are accepted as an appropriate means to differentiate and examine these psychologically different groups.[24]

PUVA Treatment Protocol

Photochemotherapy (PUVA) is a widely used treatment for psoriasis and combines long-wavelength (320-390 nm) UV-A irradiation with methoxsalen (8-methoxypsoralen). This is an orally administered photosensitizer taken at a dose of 0.6 mg/kg 2 hours before UV-A therapy. In the United Kingdom, the starting dose of UV-A therapy is based on determination of the minimal phototoxic dose and skin phototype. The minimal phototoxic dose method assesses the recognized interindividual differences for skin to develop erythema and tanning after UV radiation. The PUVA therapy is administered below the threshold for such erythema.

ETHICAL APPROVAL

The study was approved by the Salford and Trafford and City of Dublin local research ethics committees, and all participants provided written, informed consent.

STATISTICAL ANALYSIS

Unless otherwise indicated, data are expressed as mean ± SD. We used the *t* test and the χ^2 test in the initial exploration of the data. The principal question was addressed by the use of the Cox proportional hazards regression analysis.[28] We analyzed differences between event curves by means of the log rank test. All summary data are provided as mean ± SD.

POWER ANALYSIS

Previous standardized assessment of worry in patients attending the psoriasis specialist clinic have suggested that approximately one third of the sample will have high worry scores. As such, and taking 2 low-level worriers as controls for each high-level worrier, a total of 90 patients would be required for the study (90% power; 5% significance).

RESULTS

Figure 1 details the flow of patients into the study. Ten patients were withdrawn from the study because of nonattendance for appointments and incomplete assessments. The final sample consisted of 112 patients with psoriasis (40 women [36%] and 72 men [64%]). The patients were aged 20 to 70 years (mean age, 43.3 ± 13.2 years) and had psoriasis for 1 to 40 years (mean duration, 19.7 ± 11.4 years), with an age at onset of psoriasis from 2 to 62 years (mean age, 22.8 ± 13.7 years). Clini-

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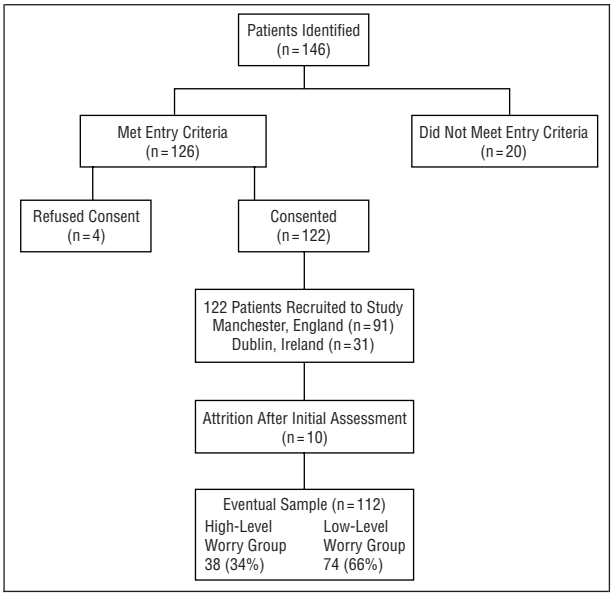

Figure 1. Flow of patients into the study.

Table 1. Characteristics of Patients Classified as Low- or High-Level Worriers at Study Entry*

Variable	Worry Group: Low Level (n = 74)	Worry Group: High Level (n = 38)
Age, y	45 ± 14	41 ± 11
Sex, No. (%)		
Male	52 (72)	20 (28)
Female	22 (55)	18 (45)
Family history of psoriasis		
Present	30 (56)	24 (44)
None	44 (76)	14 (24)
Duration, y	20 ± 12	19 ± 11
Age at onset of psoriasis, y	24 ± 14	21 ± 11
Clinical severity of psoriasis†	11.6 ± 5.6	12.1 ± 5.8
Skin phototype, No. of patients		
I	5	7
II	32	12
III	35	16
IV	2	3
Alcohol intake, U/wk‡	13 ± 13	9 ± 10
Anxiety score§	6 ± 4	14 ± 4
Depression score§	4 ± 3	8 ± 5

*Unless otherwise indicated, data are expressed as mean ± SD.
†Determined by means of the Psoriasis Area and Severity Index.[19]
‡A unit of alcohol equaled approximately 275 mL of standard-strength beer or lager, 125 mL of wine, or 25 mL of spirits.
§Determined by means of the Hospital Anxiety and Depression Scale.[22]

cal severity of psoriasis, as assessed by means of the PASI, ranged from 2.4 to 28.1 (mean score, 11.5±5.4). Scores on the Hospital Anxiety and Depression Scale ranged from 0 to 21 for anxiety (mean score, 8.8±5.1), and 0 to 21 for depression (mean score, 5.2±4.2). When we used the documented cutoffs on the worry measure to differentiate between low-level, nonpathological (PSWQ≤60) and high-level pathological (PSWQ>60) worry,[24,25] 34% of patients scored in the pathological or high-level worry category. This finding is consistent with previous research on levels of worry in patients with psoriasis attending outpatient clinics.[25,29] **Table 1** shows the demographic data and baseline variables for participants as a function of the categories of high- and low-level worry.

COMPARISON OF DATA FROM THE DUBLIN AND MANCHESTER COHORTS

Examination of data from the Manchester and Dublin cohorts showed them to be similar. The patients from the 2 centers did not significantly differ in time to clearance of psoriasis, patient age, age at onset of psoriasis, duration of psoriasis, alcohol intake, or anxiety or depression scores ($t<1.37$; $P=.17$). Similarly, both cohorts did not significantly differ in the proportion of patients who were high-level worriers, in skin type classifications, or in the numbers of male and female patients ($\chi^2<1.28$; $P=.26$). The only significant difference between the patients from the 2 centers was that the Dublin cohort had more severe psoriasis at the start of PUVA therapy ($t=-3.14$; $P=.02$; mean cohort scores, 14.1±5.8 vs 10.6±5.1).

INITIAL EXAMINATION OF THE WORRY GROUPS

The high-level worry group did not differ from the low-level worry group in terms of age, duration of psoriasis, age at onset of psoriasis, weekly alcohol intake, or severity of psoriasis ($t<1.60$; $P=.11$). We found a trend for women to be overrepresented in the high-level worry category, although this failed to reach statistical significance ($\chi^2=3.40$; $P=.06$). Although patients who had no family history of psoriasis showed the usual distribution of worry (approximately 33% high-level worry), patients with a family history of psoriasis showed an equal distribution between worry categories (low-level worry, 52%; high-level worry, 48%). This represented a significant result ($\chi^2=5.48$; $P=.02$) and suggests that more high-level worriers were from families in which first-degree relatives also had psoriasis.

Of the 112 patients who remained in the study, 90 achieved clearance of their psoriasis during the course of PUVA. Patients who had an optimal response to PUVA showed a range of clearance times varying from 28 to 144 days (median, 81 days). To examine which baseline factors were the best predictors of time to clearance, we used a time-to-event method (Cox proportional hazards model).[28]

TIME TO CLEARANCE OF PSORIASIS

The different baseline factors entered into the proportional hazards model are shown in **Table 2**. The only significant variable predictive of time to clearance of psoriasis was pathological/high-level worry (score statistic, 6.34; $P=.01$). No other factor showed any predictive power in this respect. **Figure 2** displays event curves for high- and low-level worriers and shows that at the 50th percentile, the time to clearance of psoriasis for low-level worriers was 19 days less than that for high-level worriers. We analyzed event curves for the high- and low-level worry groups by means of the log rank test, which showed a significant difference for the high- and low-level worry groups (log rank, 6.64; $df=1$; $P=.01$). The rela-

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tive risk (ExpB) associated with the high-level worry group was 1.81 (95% confidence interval, 1.13-2.90). Thus, patients in the high-level worry group experienced clearance with PUVA treatment at a rate 1.8 times slower than their low-level worry counterparts

Of the 22 patients who did not achieve clearance of their psoriasis with PUVA therapy, 8 (36%) were low-level worriers and 14 (64%) were high-level worriers. This finding suggests that high-level worry may slow the effectiveness of PUVA and even abrogate its effectiveness altogether.

COMMENT

This study shows that psychological distress, in the form of excessive worrying, significantly slows the rate of clearance of psoriasis in patients undergoing standard therapy with PUVA. Patients who had high levels of worry (34% of the sample as defined by the PSWQ) were almost twice as likely not to achieve clearance of their psoriasis within a similar length of time as those with low levels of worry. The median difference to clearance between low- and high-level worry groups was 19 days. Patients in the high-level worry group did not have greater clinical levels of psoriasis or a longer-term course of the condition at entry into the study. This observation is consistent with previous findings about the correlates of worry in psoriasis.[25,29] The lack of any other clinical or demographic differences between the low- and high-level worry groups, with the exception of family history, adds to the robustness of this finding.

Although it is difficult to identify the precise mechanism by which psychological distress, in the form of worrying, has an effect on the disease process in psoriasis, some evidence suggests that worry may modulate autonomic activity. Compared with controls, excessive worriers show reduced response (in terms of skin conductance) to experimentally induced stress, a slower habituation to such stress,[30] and a much slower return to baseline for skin conductance and heart rate.[31] Psychological distress before medical school examinations has a significant detrimental effect on the barrier function of the epidermis, thereby allowing increased transepidermal water loss and susceptibility to dermatitis and perhaps psoriasis.[8] Psoriasis is a single example of such phenomena; alopecia areata,[32] atopic dermatitis,[33] and acne vulgaris[34] are all well-documented skin diseases that can also be triggered by stressful life events and perhaps made resistant to therapy by continuing stress. The clinical significance of such observations is pertinent to long-term therapy. In the context of nondermatological disease, chronic worrying has been shown to be a significant risk factor for myocardial infarction at 20-year follow-up in the Normative Aging Study.[35] In rheumatoid arthritis, a disease with pathomechanisms similar to psoriasis, worry is a strong predictor of poor functional status at the 1-year follow-up.[36] Worry is also the principal predictor of immune system dysregulation in survivors of a natural disaster, beyond related concepts such as increased intrusive thoughts, avoidance of trauma-related stimuli, anxiety, or changes in health behavior.[37] The current findings are commensurate with these observations and underscore the complex interplay between physiology and psychology. The management of any chronic disease such as psoriasis must take account of the biopsychosocial model.

As we[38] and others[39] have previously noted, severity of psoriasis is not merely a reflection or an index of physical extent of disease, but is also dictated by psychosocial disability in that individual. It appears from this study that this concept needs to extend beyond mere definition to its potential resistance to conventional therapy such as PUVA. Like all current treatments for psoriasis, PUVA is very effective but does not cure the disease. Approximately 50% of treated patients will experience relapse of their psoriasis within 6 months.[20] Investigations of whether patients with high-level worry are also

Table 2. Results of Cox Proportional Hazards Analysis on PUVA-Induced Time to Clearance of Psoriasis

Variable	Score Statistic	Degrees of Freedom	*P* Value
Pathological/high-level worry	6.34	1	.01
Anxiety	2.53	1	.11
Duration of psoriasis, y	2.13	1	.14
Clinical severity of psoriasis	1.48	1	.22
Skin types	1.16	3	.76
I	0.21	1	.64
II	0.03	1	.85
III	0.31	1	.57
Alcohol intake per week	0.93	1	.33
Family history of psoriasis	0.71	1	.31
Depression	0.49	1	.48
Sex	0.02	1	.88
Age	0.01	1	.90

Abbreviation: PUVA, psoralen-UV-A.

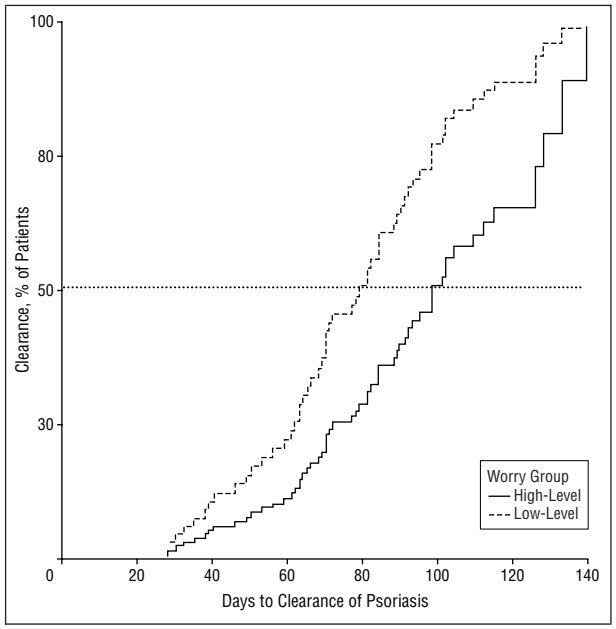

Figure 2. The Cox proportional hazards event curves for patients in the high- and low-level worry groups and time to clearance of psoriasis after treatment with psoralen–UV-A. Patients in the high-level worry group (n=38) took longer (*P*=.01) to achieve clearance of their psoriasis than those in the low-level worry group (n=74).

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significantly overrepresented in this relapse group are needed. One strategy could be to identify patients with high-level worry (using the PSWQ) before starting PUVA therapy. These individuals could be treated more assiduously, perhaps with the use of cognitive behavior therapy or mindfulness stress reduction techniques that have shown some early promise.[16,17] This resistance to therapy may also constitute a potential confounder in clinical trials of new medicines for treatment of psoriasis. How worry may heighten resistance to therapy is currently unknown. Perhaps reduced cortisolic responses coupled with stimulation of cutaneous T-cell trafficking[40] play a role, as has been demonstrated in experiments in mice whereby an allergic contact dermatitis response is enhanced in stressed animals.[41] These findings provide further evidence of the existence of a brain-skin axis. Focus on this fascinating area is needed to identify potential mechanisms and to encompass a holistic approach to the treatment of chronic inflammatory skin disease.

Accepted for publication October 23, 2002.

This study was supported by grant RG1/01 from the Psoriasis Association of Great Britain and Ireland, Northampton, England.

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