

Treatment of Atopic Dermatitis and Psoriasis Vulgaris With Bupropion-SR: A Pilot Study

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Objective: To determine whether the antidepressant bupropion may be useful in treating atopic dermatitis and psoriasis in nondepressed patients. **Method:** Ten nondepressed subjects with atopic dermatitis and 10 with psoriasis completed a single-track, open-label treatment protocol with bupropion-SR in doses of 150 mg/day and 300 mg/day, administered sequentially for 3 weeks each, followed by a 3-week wash-out. Treatment response was assessed at the end of each 3-week period. **Results:** Six of the 10 subjects with atopic dermatitis showed a reduction in affected body surface area by the end of 6 weeks of bupropion treatment, with affected area increasing toward the prestudy baseline in all responders following bupropion discontinuation—a highly significant treatment effect ($p = .0003$). Of the 10 subjects having psoriasis, improvement over baseline after 6 weeks of treatment was seen in eight subjects, with coverage increasing toward the prestudy baseline in the responders following bupropion discontinuation ($p = .001$). Average reduction in affected area in the responders at week 6 of treatment was approximately 50% in both groups. **Conclusions:** The generally good tolerability and relative safety of bupropion-SR makes a trial of this agent worthwhile in patients with atopic dermatitis or psoriasis who have failed treatment with more conventional medications. Normalization by bupropion of potentially causative neuroendocrine, immunologic, or catecholaminergic abnormalities in both of these dermatologic disorders is a possible mechanism of action for the observed salutary effects of this drug on our subjects' skin disease. **Key words:** antidepressant, atopic dermatitis, bupropion, eczema, psoriasis.

ANCOVA = analysis of covariance; bupropion-SR = bupropion sustained-release formulation (Glaxo-SmithKline Pharmaceuticals); DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; hCRH = human corticotrophin-releasing hormone; HPA = hypothalamic-pituitary-adrenal.

In a recent study assessing the efficacy of the aminoketone antidepressant bupropion-SR (1) (Wellbutrin-SR, GlaxoSmithKline) as a treatment for orgasmic dysfunction in nondepressed individuals (2), one of our subjects who had suffered from treatment-refractory atopic dermatitis (eczema) for about 15 years noted an unexpected and unprecedented clearing of all skin disease after about 5 weeks on 150–300 mg/day of the bupropion and a subsequent return of the dermatitis to its previous severity about 3 weeks after bupropion was discontinued. Although a call to the drug's manufacturer regarding these findings revealed that they had received a few sporadic reports of patients with atopic dermatitis and also psoriasis vulgaris (henceforth, psoriasis) whose skin had cleared

during treatment with bupropion, no reports of the effect of bupropion on dermatologic disorders could be found in the medical literature. There have, however, been published reports of improvement of atopic dermatitis with topical application of the strongly antihistaminergic tricyclic antidepressant doxepin (3, 4) and of psoriasis with oral administration the tricyclic antidepressant imipramine (5, 6) and with the monoamine-oxidase inhibitor moclobemide (7).

In an effort to determine whether orally administered bupropion might indeed have beneficial effects on skin disease in nondepressed patients with atopic dermatitis and psoriasis, we conducted the following pilot study.

METHODS

Adult subjects with atopic dermatitis or psoriasis diagnosed by a dermatologist were eligible to participate in this study if their skin disease had been present continuously for at least 1 year, had not changed in intensity or coverage during the 3 months preceding the study, and had not previously cleared with topical treatment. Excluded from participation were subjects using oral or topical dermatologic medications within the preceding month; subjects having any signs or symptoms of depression, anxiety disorder, mania, psychosis, or history thereof (DSM-IV criteria (8)); subjects having any major medical illness, epilepsy, or eating disorder; and subjects taking any antidepressant medication. Specifically with regard to depression, no subject reported depressed mood and no subject had more than one of the nine required DSM-IV criteria for depression (8). The study was approved by the university's investigational review board, and informed consent was obtained from all study subjects.

Thirteen subjects having atopic dermatitis and 11 with psoriasis were inducted into the study. Of the three subjects with atopic dermatitis who did not complete the study, one failed to return after the initial visit, citing inconvenience as the reason, and two failed to return after the second visit despite both reporting that the bupropion was helpful (one cited inconvenience and the other moved

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from the area). Of the subjects with psoriasis, 10 completed the study: the one noncompleter failed to return after the first visit and did not return our follow-up calls. Subject characteristics of the 20 completers included in the data analysis are shown in Table 1 (atopic dermatitis) and Table 2 (psoriasis). The median duration of continuous disease presence before participation in subjects with atopic dermatitis was 10 years (range 1–15 years) and, in subjects with psoriasis, 20 years (range 3–45 years).

The study was designed as a single-track, open-label protocol of two sequential doses of bupropion-SR followed by medication discontinuation over a period of 9 weeks. At the time of the initial evaluation, medical, psychiatric, and dermatologic histories were obtained and the skin was examined with attention to disease appearance and percent coverage of the affected body area(s) as measured to the closest 25% (Table 1 and Table 2). Also recorded was whether the subjects believed their skin disease worsened under psychological stress.

Subjects were then placed on bupropion-SR 150 mg by mouth each morning for 3 weeks, at which time the subjects returned to the clinic for evaluation of drug effect. Bupropion-SR dosage was then increased to 150 mg by mouth twice daily until the second follow-up visit 3 weeks later; subjects who felt that 150 mg/d was adequate or were having any bothersome side effects, however, had the option of remaining on 150 mg daily for the second dosing period. At the time of the second follow-up visit (week 6 of the study), the skin was reexamined and the bupropion was discontinued. The final clinical evaluation occurred 3 weeks following bupropion discontinuation (week 9). Qualitative changes in skin condition by examination and patient report were recorded for each subject, and changes in measured affected surface area were rated relative to that observed at the initial evaluation as closest to a $\geq 75\%$ reduction (-3), 50% reduction (-2), 25% reduction (-1), no change (0), 25% increase ($+1$), 50% increase ($+2$), or $\geq 75\%$ increase ($+3$). Additionally, subjects were asked at each follow-up visit whether any psychiatric symptoms, particularly those of depression, had emerged.

Outcome data regarding changes in skin condition as well as potential covariate effects (age, sex, race, extent of disease coverage, whether or not the subjects considered their dermatitis to be stress related, duration of the dermatitis before study participation, and bupropion dose) were analyzed using a one-way, repeated-measures ANCOVA model for treatment effect (SAS procedure MIXED). An autocorrelation (AR (1)) structure was incorporated into the analysis

to adjust for possible nonindependence of the within-subjects observations in this longitudinal data (9). Tests of treatment effect were one sided; covariate analyses were two sided.

RESULTS

Quantitative changes in affected surface area relative to the prestudy baseline are shown in Table 3 (atopic dermatitis) and Table 4 (psoriasis). Of the 10 subjects having atopic dermatitis, observable decreases relative to baseline in affected surface area after 3 weeks on bupropion-SR 150 mg/day were rated as closest to 25% in three, and one subject's skin disease cleared entirely (subject A4); no effect was observed in six subjects ($t_{27} = 1.8$, $p = .04$ for week 3 vs. baseline). Three weeks later, with eight subjects taking 300 mg/day bupropion-SR and two remaining on 150 mg/day, 6 of the 10 subjects showed decreases in affected surface area over baseline, three of which were rated as 50% and three as $\geq 75\%$; four subjects' disease remained unchanged, and the one subject whose disease cleared entirely at week 3 had a return of one small patch of dermatitis by week 6 ($t_{27} = 4.6$, $p < .0001$ for week 6 vs. baseline; $t_{27} = 2.8$, $p = .005$ for week 6 vs. week 3). Average reduction in affected surface area at week 6 in the responders was approximately 50%. In all cases, decreases in affected surface area were associated with subjective reports of improvement in disease coverage, intensity, irritation, and pruritus.

Three weeks following discontinuation of the bupropion-SR, each of the subjects whose atopic dermatitis improved on the medication showed an increase in affected surface area over that present at week 6, with skin disease in three of these subjects returning to its prestudy condition ($t_{27} = -3.7$, $p = .0005$ for week

TABLE 1. Demographic and Clinical Characteristics of Subjects Having Atopic Dermatitis^a

Subject	Age	Sex	Race ^a	Disease Description: Percent Coverage of Affected Body Area and Location	Stress Related?	Duration ^b (years)
A1	24	F	B	25% antecubital, legs	No	15
A2	24	F	W	25% scalp	Uncertain	14
A3	27	M	W	25% trunk, arms	No	1
A4	20	F	B	50% forehead, back, dorsa of hands, flexor surfaces of knees and elbows	No	2
A5	27	F	B	25% back of neck, sternum, wrists	No	23
A6	48	M	W	25% thumbs	No	7
A7	27	M	A	25% back, ankles, wrists, behind knees (numular type)	Yes	14
A8	25	F	W	50% lower half posterior scalp	No	11
A9	40	F	W	25% right hand and fingers; right leg	Yes	1
A10	22	F	B	50% neck, abdomen, chest, dorsa of hands, legs	Yes	2

^a B = black; W = white; A = Asian.

^b Duration of continuous disease presence before study participation.

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TABLE 2. Demographic and Clinical Characteristics of Subjects Having Psoriasis^a

Subject	Age	Sex	Race ^a	Disease Description: Percent Coverage of Affected Body Area and Location	Stress Related?	Duration ^b (years)
P1	59	F	W	75% palms and soles	Yes	18
P2	52	F	W	50% scalp, ears, pubic; 75% extensor surface elbows and knees	No	20
P3	42	F	B	25% legs, elbows, forearms, trunk, scalp	No	10
P4	51	M	W	25% lower legs, scalp, elbows	No	20
P5	24	F	W	25% elbows, knees, scalp	Yes	15
P6	53	M	W	50% legs, trunk, elbows; 25% face	No	15
P7	33	M	W	75% elbows, knees; 50% pretibial	Yes	25
P8	26	M	W	50% scalp, neck, face, trunk, arms	No	3
P9	52	F	W	25% arms, trunk, scalp	No	40
P10	52	M	W	25% scalp, groin, perianal, thighs, back	No	40

^a B = black; W = white; A = Asian.

^b Duration of continuous disease presence before study participation.

TABLE 3. Change Scores for Disease Coverage Relative to Baseline at Each Evaluation Period for Patients With Atopic Dermatitis; $\geq 75\%$ Reduction (-3), 50% Reduction (-2), 25% Reduction (-1), No Change (0), 25% Increase (+1), 50% Increase (+), or $\geq 75\%$ Increase (+3)

Subject	Week 3 Change Score ^a	Week 6 Change Score ^c	Week 9 Change Score
A1	0	-3	0
A2 ^d	-1	-2	0
A3	0	-3	-1
A4 ^d	-3	-3	-2
A5	0	0	0
A6	0	0	0
A7	0	0	0
A8	-1	-2	-1
A9	-1	-2	0
A10	0	0	+1

^a Bupropion-SR (150 mg/day). $p = .04$ vs. baseline.

^b Bupropion-SR (300 mg/day). $p < .0001$ vs. baseline, $p = .005$ vs. week 3.

^c Bupropion-SR (3 weeks off). $p = .0005$ vs. week 6, $p = .37$ vs. baseline.

^d Subject elected to remain on 150 mg/day of bupropion-SR throughout the dosing period.

9 vs. week 6; $t_{27} = -0.92$, $p = .37$ for week 9 vs. baseline). Skin disease in three subjects remained unchanged throughout the 9-week protocol, and one subject's disease remained unchanged during bupropion administration yet increased in affected area by approximately 25% following its discontinuation. An overall treatment effect was highly significant ($F_{3,27} = 7.9$, $p = .0003$). There were no significant correlations between treatment effect and age, sex, race, extent of disease coverage, whether or not the subjects considered their skin disease to be stress related, duration of the skin disease before study participation, or bupropion dose.

Three of the six subjects who appeared to have a positive response to bupropion expressed a desire to

TABLE 4. Change Scores for Disease Coverage Relative to Baseline at Each Evaluation Period for Patients With Psoriasis^a

Subject	Week 3 Change Score ^a	Week 6 Change Score ^b	Week 9 Change Score ^c
P1	+1	-3	0
P2 ^d	-2	-3	+1
P3	-1	-2	-1
P4	0	-2	-1
P5	-3	-1	0
P6	0	0	0
P7	0	-1	0
P8	0	-1	0
P9	0	-3	-1
P10	0	0	0

^a Bupropion-SR (150 mg/day). $p = .11$ vs. Baseline).

^b Bupropion-SR (300 mg/day). $p = .0002$ vs. Baseline, $p = .005$ vs. week 3).

^c Bupropion-SR (3 weeks off). $p = .001$ vs. Week 6, $p = .62$ vs. Baseline).

^d Subject elected to remain on 150 mg/day bupropion-SR throughout the dosing period.

resume the medication for long-term treatment of their atopic dermatitis; those who did not expressed dislike of "dependence on [systemic] medication." One of these responders (A1) was subsequently treated with bupropion 300 mg/day by the first author and remained disease free at a 3-month follow-up.

Of the 10 subjects having psoriasis, observable decreases in affected surface area relative to baseline after 3 weeks on bupropion-SR 150 mg/day were rated as closest to 25% in one, 50% in one, and $\geq 75\%$ in one; one subject's disease increased in surface area by 25%, six were unchanged, and no subject's skin disease cleared entirely ($t_{27} = 1.24$, $p = .11$ for week 3 vs. baseline). Three weeks later, with nine subjects taking 300 mg/day bupropion-SR and one remaining on 150 mg/day, 8 of the 10 subjects showed decreases in af-

affected surface area over baseline, three of which were rated as 25%, two as 50%, and three as $\geq 75\%$; skin disease in two subjects remained unchanged ($t_{27} = 4.0$, $p = .0002$ for week 6 vs. baseline; $t_{27} = 2.7$, $p = .005$ for week 6 vs. week 3). Average reduction in disease coverage at week 6 in the responders was approximately 50%. In all cases, decreases in affected surface area were associated with subjective reports of improvement in disease coverage, intensity, irritation, and pruritus.

Three weeks following discontinuation of the bupropion-SR, each of the subjects whose psoriasis improved on bupropion-SR showed an increase in affected surface area over that present at week 6, with skin disease increasing to its baseline condition in four of these subjects and exceeding baseline coverage by about 25% in one ($t_{27} = -3.5$, $p = .001$ for week 9 vs. week 6; $t_{27} = 0.50$, $p = .62$ for week 9 vs. baseline). Skin disease in two subjects remained unchanged and no subject's disease cleared completely during the study period. An overall treatment effect was highly significant ($F_{3,27} = 6.3$, $p = .001$). As with subjects having atopic dermatitis, there were no significant correlations between treatment effect and any of the covariates.

Six of the eight subjects whose psoriasis responded positively to bupropion-SR expressed a desire to resume the medication for long-term treatment of their psoriasis; again, those who did not cited dislike of long-term oral medication use. Of the two of these six subjects who were personally treated by the first author, the initial benefit waned after about 3 months in one (P2), but in the other (P1), there was complete clearing of all skin disease 1 month after resuming the medication and—save for one small plaque—the psoriatic lesions have yet to return after 19 months.

The bupropion-SR was generally well tolerated, and no subjects dropped out due to side effects. Specific side effects that occurred in more than 1 of the 20 subjects were limited to dizziness ($N = 2$), restless sleep or increased dreaming ($N = 2$), subjective tachycardia ($N = 3$), and feeling “jittery” or “wired” ($N = 3$). Only one subject (P8) felt that the bupropion improved his mood beyond his nondepressed baseline; no other subject reported any change in mood or the emergence of depressive symptoms.

DISCUSSION

That a highly significant treatment effect was found, with skin disease in 6 out of 10 subjects with atopic dermatitis and 8 out of 10 with psoriasis improving by week 6 of this study and all of the responders in both groups worsening within 3 weeks of discontinuing

bupropion, suggests that orally administered bupropion may be useful in treating both of these disorders. Also arguing for a significant drug effect is that the observed improvements occurred in patients with very chronic, relatively static skin disease that had not previously responded well to topical treatment and also that one subject with particularly severe psoriasis for 18 years remains nearly disease free 19 months into bupropion treatment. The absence of a control group and blinding in this study does not, however, allow exclusion of a significant placebo response. That no significant correlations were found between treatment effect and age, sex, race, extent of disease coverage, whether or not the subjects considered their dermatitis to be stress related, duration of the dermatitis before study participation, and bupropion dose is noteworthy, but the number of subjects is too small to conclude that these factors are indeed inconsequential.

A mechanism of action for the observed improvements is difficult to postulate because bupropion has no known effect on skin, its only known action being a weak inhibitor of norepinephrine and dopamine uptake in the brain (1, 10, 11). Although many studies have shown a higher rate of anxiety, depression, intrapsychic conflict, and perceived stress levels in patients with both atopic dermatitis and psoriasis (12–20), the absence of an association in this study between improvement and whether subjects perceived their dermatitis to be stress related as well as the absence of a general effect of bupropion on subject mood would argue against improvement being related to a specific antidepressant or psychological effect of bupropion.

More plausible, however, are potential neuroendocrine, immunologic, or catecholaminergic mechanisms of action for bupropion on these skin disorders. Several studies have shown that a number of antidepressants have neuroendocrine and immunologic effects, including decreasing natural-killer cell activity and inflammatory response in mice; decreasing macrophage migration and hypersensitivity reactions in rats (21–24); and in humans, altering concentrations of opioid peptides and beta-endorphin concentrations in lymphocytes (25), suppressing natural-killer cell activity (26), altering interferon/interleukin production ratios (27), normalizing the chronic hypothalamic-pituitary-adrenocortical (HPA) axis overactivity in patients with depression (21, 28–30), and inhibiting the substance-P inflammatory response in skin (31). Such findings, however, have not yet been specifically demonstrated with bupropion. Additionally, the antidepressants, including bupropion, have been shown to enhance central noradrenergic transmission by decreasing the sensitivity of postsynaptic alpha-2 adren-

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ergic receptors (32) and decreasing the firing rates of noradrenergic neurons in the locus ceruleus (1) while reducing whole-body turnover of norepinephrine (33) and plasma levels of norepinephrine and its metabolites 3-methoxy-4-hydroxyphenylglycol and dihydroxyphenylglycol (1, 32, 34–36).

Interestingly, neuroendocrine, immunologic, and catecholaminergic abnormalities have all been implicated in the pathogenesis of both atopic dermatitis and psoriasis. Patients with atopic dermatitis show an attenuated response of the hypothalamic-pituitary-adrenal system during a human corticotrophin-releasing hormone (hCRH) challenge (37), increased IgE-production and mediator secretion and T-lymphocyte regulatory disturbances (38, 39), and decreased natural-killer cell function (40). Catecholaminergic abnormalities in atopic dermatitis include impaired beta-adrenergic and enhanced alpha-adrenergic reactivity (41, 42), elevated plasma levels of norepinephrine (43, 44), and an abnormally low density of beta-2-adrenergic surface receptors on skin keratinocytes (45). As these receptors respond to circulating catecholamines by regulating calcium influx and thereby controlling cell differentiation (45), such systemic or cellular abnormalities could give rise to the abnormal epidermal development observed in atopic dermatitis. It is also not inconceivable that, because both the skin and brain are derived from embryologic cell populations adjacent to the neural crest (46), there is enough commonality between these tissues that bupropion may have specific effects of its own on adrenergic receptors in dermal or epidermal tissue. Hypocortisolism and abnormalities in the function of the HPA axis (47), abnormalities in T-lymphocyte reactivity and release of associated inflammatory cytokines in the skin (48–51), and relatively high concentrations of circulating norepinephrine (52) have also been observed in patients with psoriasis. Additionally, there is increasing evidence that abnormalities in neurotensin and substance-P receptors or production in the skin may be involved in the pathogenesis of both atopic dermatitis and psoriasis (53, 54).

Normalization by bupropion of any of these potentially causative abnormalities in atopic dermatitis and psoriasis is thus theoretically possible and may explain the observed salutary effects of this drug on our subjects' skin disease. At this time, however, each of these mechanistic possibilities must be considered speculative and it is not possible to narrow them much further; if, however, it can be shown that noncatecholaminergic antidepressants (such as the selective-serotonin reuptake inhibitor antidepressants) also have a beneficial effect in these disorders, then a catecholaminergic mechanism of action for bupropion in

these dermatologic disorders would be considerably less likely.

Further research will be necessary to confirm our findings and to clarify possible mechanisms of action for the observed dermatologic effects of bupropion-SR in this study. Until such time that these can be completed, however, we believe that the generally good tolerability and relative safety of bupropion-SR makes a trial of this agent worthwhile in patients with atopic dermatitis or psoriasis who have failed treatment with more conventional medications.

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