Comorbidities significantly impact patients' preferences for psoriasis treatments

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Background: Non-adherence rates are high among patients with psoriasis, partly because of discordance between recommended treatments and individual preferences.

Objectives: Our aim was to assess the impact of comorbidities on patients' preferences for psoriasis treatments.

Methods: A computer-based conjoint analysis experiment was conducted to analyze preferences of patients with psoriasis (N = 163) for treatment outcome attributes (probability, magnitude and duration of benefit; probability, severity and reversibility of side effects) and process attributes (treatment location, frequency, duration, delivery method, individual cost). The impact of comorbidities (psoriatic arthritis, cardiovascular disease, diabetes, and depression) on relative importance scores of each attribute was assessed by analyses of variance, post hoc test, and multivariate regression analysis.

Results: Among the participants included (58.9% males, mean age 49.3 yrs), 27% suffered from psoriatic arthritis, 13.5% from cardiovascular disease, 8% from diabetes, and 12.9% from depression. Preferences for treatment attributes varied significantly depending on comorbidities. Participants with psoriatic arthritis cared most about the probability of benefit (β 0.166; P = .037), whereas those participants with cardiovascular disease were highly concerned about the probability of side effects (β 0.179; P = .046). For participants with depression, treatment duration (β 0.163; P = .047), and individual cost (P = .023) were highly important.

Limitations: Only patients with moderate and severe psoriasis treated at a university medical center were included.

Conclusions: Integrating patients' preferences into shared decision-making may facilitate treatment adherence and optimize outcomes. Addressing patients' comorbidities, particularly depression, may be a currently neglected opportunity to improve care. (J Am Acad Dermatol 2012;67:363-72.)

Key words: adherence; cardiovascular disease; conjoint analysis; depression; diabetes; preferences; psoriasis; psoriatic arthritis.

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INTRODUCTION

Psoriasis is known to cause considerable physical impairment, but also severe reduction in health-related quality of life.[1] Recently it has been highlighted that psoriasis is associated with a variety of comorbidities. Up to one fourth of patients develop psoriatic arthritis.[2] Furthermore, patients with psoriasis are at increased risk for metabolic and cardiovascular comorbidities, in particular metabolic syndrome, diabetes, ischemic heart disease, myocardial infarction, and stroke.[3-9] On the one hand, psoriasis is associated with a tendency toward unhealthy behaviors, with markedly increased prevalence of smoking and obesity among affected patients.[10-12] On the other hand, psoriasis has been proposed to influence metabolic and cardiovascular risk independently of lifestyle factors, that is, through shared genetic risks and mutual inflammatory pathways.[13,14]

A serious, but often neglected, comorbidity is compromised mental health status. Psoriasis is strongly associated with depression, anxiety, and suicidality.[15] For example, in a recent population-based study, 12.5% of patients with severe psoriasis reported a history of depression, as compared with 4.7% in the control population.[16]

A wide range of treatment options are available for psoriasis, including a variety of local therapies, phototherapy, traditional systemic antipsoriatic medications (acitretin, fumaric acids, methotrexate, and cyclosporine), and biologicals. However, non-adherence to treatment has been reported in up to 40% of patients with psoriasis, leading to poor clinical outcome and elevated risk for comorbidities.[17] This high rate of non-adherence is partly explicable by the fact that certain treatments may not be compatible with patients' preferences, their personal and professional life. Assessment of patients' preferences and individual circumstances is therefore important in identifying the needs and hazards that feed into non-adherence.[18]

CAPSULE SUMMARY

- Treatment dissatisfaction and non-adherence is high among psoriasis patients. Adherence may be improved by integrating preferences into shared decision making.
- Using conjoint analysis exercises we found that comorbidities significantly impact preferences. Psoriasis patients with cardiovascular disease are highly concerned about side effects, patients with depression about treatment duration and individual cost.
- Integrating patients' preferences into shared decision-making may facilitate adherence and optimize outcomes. Addressing patients' comorbidities, particularly depression, may be a currently neglected opportunity to improve care.

Treatment preferences of patients with psoriasis have been investigated in a number of studies using time trade-off, willingness-to-pay, and standard gamble methods, as well as visual analogue scales.[19-22] Another approach to assess preferences is conjoint analyses in which participants have to choose between treatment options, resembling actual decision-making.[23-25] Conjoint analysis exercises force trade-offs in a choice context and allow quantification and comparison of attributes related to treatment outcomes and processes.

In our previous study we used conjoint analysis to assess patients' preferences for psoriasis treatments and the impact of sociodemographic and socioeconomic characteristics on preferences.[26] We observed that patients were most concerned about attributes associated with treatment processes, in particular treatment location, and that they were willing to trade side effects both for a better therapeutic outcome and for process attributes compatible with their personal and professional life. Comorbidities, such as psoriatic arthritis, cardiovascular disease, diabetes, and depression, can be heavily debilitating factors with great impact on daily life. Therefore we decided to investigate the influence of comorbidities on treatment preferences using the same approach and patient cohort as in our previous study.

SUBJECTS AND METHODS

Study participants

Patients with psoriasis who are 18 years of age or older visiting outpatient clinics at the Dermatology Department of the University Hospital Mannheim between December 2009 and September 2010 were asked to participate. To ensure that the full range of antipsoriatic treatment options (topical therapy, phototherapy, traditional systemic antipsoriatic medications and biologicals) could be valid options, only patients with moderate to severe psoriasis according to the criteria of the Committee for Medicinal Products for Human Use were recruited,[27] including patients with (1) a Psoriasis

Abbreviations used:

ANOVA: analysis of variance
CA: conjoint analysis
CASPAR: classification criteria for the diagnosis of psoriatic arthritis
DLQI: Dermatology Life Quality Index
PUVA: psoralen plus ultraviolet A
PASI: Psoriasis Area and Severity Index
RIS: relative attribute importance score
SD: standard deviation

Area and Severity Index (PASI) greater than 10[28]; (2) psoriatic involvement of the hands, feet, or head; (3) psoriatic arthritis according to Classification of Psoriatic Arthritis (CASPAR) criteria[29]; and (4) patients on systemic antipsoriatic therapy (see Tables I and II). Both patients seeking consultation for the first time and patients coming for follow-up visits were included. After providing written informed consent, participants completed a computerized survey containing the conjoint analysis exercises before consultation with the doctor. Study procedures were approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg, and the study was performed according to the principles of the Declaration of Helsinki.

Data collection

Patient preferences were evaluated using conjoint analysis exercises (CA) as described previously.[26] Briefly, currently available treatments were decomposed into 6 outcome attributes (probability, magnitude and duration of benefit; probability, severity, and reversibility of side effects) and 5 process attributes (treatment location, frequency, duration, delivery method, and cost for the individual). Four realistic levels were created for each attribute (Table III).[26] To reduce the amount of information presented in each setting, attributes were separated into two groups.[26] Cost was included in both groups to facilitate later comparison. By combining the levels of attribute group 1 or 2 in random fashion, hypothetical treatment scenarios were designed. Commercially available software (http://www.sawtoothsoftware.com/) was utilized for design of the CA exercises and survey. Preferences were measured by presenting hypothetical treatment scenarios pair-wise and asking the participants to choose their preferred option (for examples, see Schaarschmidt et al[26]).

Information on psoriatic arthritis (arthralgia: yes/no, suspected psoriatic arthritis: yes/no, prior diagnosis of psoriatic arthritis: yes/no), cardiovascular comorbidities (ischemic heart disease, myocardial infarction, stroke, or other: yes/no), diabetes (yes/no), and depression (yes/no) was self-reported in the computerized survey. The Dermatology Life Quality Index (DLQI)[30] was also included in the survey, as was smoking status (history of smoking: yes/no, current smoker: yes/no with current smoking defined as ≥ 1 cigarettes/day). The PASI was determined during physical examination by two of the investigators (A.S, and M.L.S.). If patients reported arthralgia or suspected psoriatic arthritis, CASPAR criteria were assessed to verify the diagnosis of psoriatic arthritis.

Table I. Characteristics of the study cohort (N = 163)

Sex, No. (%)	
Female	67 (41.1)
Male	96 (58.9)
Age (y), mean ± SD (range)	49.3 ± 14.1 (18-80)
PASI, mean ± SD (range)	5.6 ± 5.5 (0-32.8)
DLQI, mean ± SD (range)	
All participants	7.6 ± 6.9 (0-29)
Participants with psoriatic arthritis	6.8 ± 7.2 (0-21)
Participants with diabetes	5.5 ± 6.4 (0-24)
Participants with cardiovascular disease	6.9 ± 7.3 (0-24)
Participants with depression	9.2 ± 7.1 (0-20)
Comorbidities, No. (%)	
Psoriatic arthritis	44 (27.0)
Diabetes	13 (8.0)
Cardiovascular disease	23 (13.5)
Depression	21 (12.9)
Smoking habits, No. (%)	
Current smoker	61 (37.4)
Former smoker	59 (36.2)
Never smoked	43 (26.4)
Currently prescribed treatment, No. (%)	
Topical therapy	122 (74.8)
Phototherapy	23 (14.1)
Traditional systemic therapy	53 (32.3)
Fumaric acid	25 (47.2)
Acitretin	12 (22.6)
Methotrexate	14 (26.4)
Other	2 (3.8)
Biologicals	28 (17.2)
Adalimumab	7 (25.0)
Etanercept	8 (28.6)
Ustekinumab	5 (17.9)
Infliximab	8 (28.6)

DLQI, Dermatology Life Quality Index; *PASI*, Psoriasis Area and Severity Index; *SD*, standard deviation.

Statistical analysis

Relative attribute importance. Part-worth utilities for each attribute level were computed by

Table II. Current antipsoriatic treatment of participants suffering from psoriatic arthritis, diabetes, cardiovascular disease, or depression

Therapy	Psoriatic arthritis, n = 44	Diabetes, n = 13	Cardiovascular disease, n = 23	Depression, n = 21
Topical therapy	26 (59.1%)	9 (69.2%)	19 (82.6%)	14 (66.7%)
Phototherapy	2 (4.5%)	1 (7.7%)	1 (4.3%)	0 (0%)
Traditional systemic therapy	12 (27.3%)	3 (23.1%)	5 (21.7%)	9 (42.9%)
Fumaric acids	3 (25.0%)	2 (66.7%)	5 (100%)	4 (44.4%)
Acitretin	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)
Methotrexate	8 (66.6%)	1 (33.3%)	0 (0%)	4 (44.4%)
Other	1 (8.3%)	0 (0%)	0 (0%)	0 (0%)
Biologicals	18 (40.9%)	3 (23.1%)	6 (26.1%)	3 (14.3%)
Adalimumab	5 (27.8%)	1 (33.3%)	3 (50.0%)	2 (66.7%)
Etanercept	7 (38.9%)	0 (0%)	0 (0%)	0 (0%)
Ustekinumab	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)
Infliximab	6 (33.3%)	2 (66.7%)	3 (50.0%)	0 (0%)
No therapy	0 (0%)	0 (0%)	0 (0%)	1 (4.8%)

means of logit regression and scaled to sum to zero within each attribute.[26] Attribute importance was assessed by calculating the range between the highest and the lowest part-worth utility for each attribute. To allow comparison between different attributes, relative attribute importance was calculated as a percentage by dividing each attribute's range by the sum of all attribute ranges and multiplying by 100. A relative importance score (RIS) for each attribute was calculated for each participant individually and thereafter averaged for all participants. Subgroup analysis with respect to comorbidities (psoriatic arthritis, cardiovascular disease, diabetes, and depression) was performed with ANOVA.

Multivariate logistic regression analysis. Choice-based conjoint analysis data from Sawtooth software was imported into SPSS statistical software (www.spss.com). Relative attribute importance was defined as the dependent variable; sex, age, PASI, DLQI, psoriatic arthritis, diabetes, cardiovascular disease, and depression were independent variables. One model was created for each treatment attribute, using the function RIS = $\beta 0 + \beta 1$ sex + $\beta 2$ age + $\beta 3$ PASI + $\beta 4$ DLQI + $\beta 5$ cardiovascular disease + $\beta 6$ diabetes + $\beta 7$ depression where $\beta 0$ is a constant for neglected factors and $\beta 1$-7 are the coefficients to be estimated. To eliminate differences due to variation in the measurement units of the characteristics assessed, the standardized regression coefficient β was calculated and used to predict the influence of psoriatic arthritis, diabetes, cardiovascular disease, and depression on RIS. A positive β value indicates gain of importance, a negative β value loss of importance in case of the respective comorbidity. A P value less than .05 was regarded as significant.

RESULTS

Study participants

Out of 197 patients with psoriasis asked to participate, 16 refused, mostly because of lack of time. Eighteen patients willing to enroll were excluded because they did not fulfill the inclusion criteria. One hundred sixty-three participants with moderate to severe psoriasis (mean age 49.3 years, 58.9% males) were successfully recruited, and all participants completed the survey (see Table I). The mean PASI for the sample was relatively low (5.6, range 0-32.8), as most participants were receiving antipsoriatic treatment at the time of data collection (Table I; details on antipsoriatic treatment of participants with psoriatic arthritis, cardiovascular disease, diabetes, and depression are given in Table II. The mean DLQI for the whole cohort was 7.6 (range, 0-29), but the subgroup of participants with depression had a considerably higher mean DLQI (9.2, range 0-20; see Table I). Twenty-seven percent of the participants suffered from psoriatic arthritis according to the CASPAR criteria. Furthermore, 8% self reported diabetes; 13.5%, cardiovascular disease; and 12.9%, depression. The vast majority (73.6%) had a history of smoking and 37.4% were current smokers.

Associations between relative attribute importance and comorbidities

Treatment preferences of the whole study cohort have been previously presented.[26] Briefly, participants attached great importance to the probability of benefit (RIS = 23.77), but also to process attributes, in particular, treatment location (RIS = 26.76) and delivery method (RIS = 23.49), whereas cost to be covered by the individual (RIS = 17.60), side-effect

Table III. Outcome attributes and levels and process attributes and levels used in the conjoint analysis survey

Outcome attributes and levels	
Treatment attribute	**Attribute levels**
Probability of benefit	
I have:	1. almost a 100% chance of experiencing a significant reduction in my psoriasis. 2. about an 80% chance of experiencing a significant reduction in my psoriasis. 3. about a 60% chance of experiencing a significant reduction in my psoriasis. 4. about a 40% chance of experiencing a significant reduction in my psoriasis.
Magnitude of benefit	
I will likely experience:	1. almost a 100% reduction in the size of my psoriasis. 2. about a 75% reduction in the size of my psoriasis. 3. about a 50% reduction in the size of my psoriasis. 4. about a 25% reduction in the size of my psoriasis.
Duration of benefit	
The improvement in my psoriasis will last for:	1. 1 year or more after completing all of my treatments. 2. 6 to 8 months after completing all of my treatments. 3. 3 to 5 months after completing all of my treatments. 4. 2 weeks after completing all of my treatments.
Probability of side effects:	
There is:	1. almost a 100% chance that I will experience side effects from the treatment. 2. about a 50% chance that I will experience side effects from the treatment. 3. about a 10% chance that I will experience side effects from the treatment. 4. less than a 1% chance that I will experience side effects from the treatment.
Reversibility of side effects:	
If side effects occur, there is:	1. almost a 100% chance that I will completely recover once my treatments are stopped. 2. about an 80% chance that I will completely recover once my treatments are stopped. 3. about a 60% chance that I will completely recover once my treatments are stopped. 4. about a 40% chance that I will completely recover once my treatments are stopped.
Side effect severity	
I may experience:	1. temporary, minor discomfort on my skin. 2. constant, moderate discomfort on my skin. 3. temporary, moderate side effects that can affect more than my skin. 4. severe side effects that can affect more than my skin.

Process attributes and levels	
Treatment attribute	**Attribute levels**
Location	
My treatment will take place:	1. at home. 2. at home with a follow-up at my local doctor's office. 3. at an outpatient clinic. 4. while I stay in the hospital for 3 weeks.
Frequency	
My treatment will occur:	1. once every 3 months. 2. once every 2 weeks. 3. two times each week. 4. twice daily.
Delivery method	
My treatment will occur by:	1. applying medication on my skin. 2. taking tablets. 3. having an injection/intravenous infusion. 4. light therapy.
Duration	
Each treatment will take:	1. 5 minutes to complete. 2. 15 to 30 minutes to complete. 3. 1 hour to complete. 4. 2 hours to complete.
Cost	
I will have to pay:	1. nothing to cover the cost of my treatments. 2. an additional 50 € per month to cover the cost of my treatments. 3. an additional 100 € per month to cover the cost of my treatments. 4. an additional 200 € per month to cover the cost of my treatments.

Table IV. Multivariate linear regression models showing the influence of comorbidities on the relative importance scores (RIS) of treatment attributes*

	Outcome variables						Process variables			
	Model 1		Model 2		Model 3		Model 4		Model 5	
	Probability of benefit		Magnitude of benefit		Probability of side effects		Method of delivery		Duration	
	Beta†	*P*‡	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
Psoriatic arthritis	**0.166**	**.037**	0.047	.564	−0.080	.320	−0.098	.230	0.001	.995
Diabetes mellitus	−0.098	.243	0.049	.569	−0.160	.062	−0.058	.501	0.027	.758
Cardiovascular disease	0.072	.410	−0.132	.139	**0.179**	**.046**	−0.074	.410	−0.018	.840
Depression	−0.039	.625	**−0.196**	**.017**	0.059	.464	0.047	.563	**0.163**	**.047**

Values given in boldface type indicate significant findings.

*Relative attribute importance was defined as the dependent variable, sex, age, Psoriasis Area and Severity Index, Dermatology Life Quality Index, psoriatic arthritis diabetes, cardiovascular disease, and depression were independent variables.

†Beta is the standardized regression coefficient. A positive beta value indicates that an attribute becomes more important; a negative beta signifies that the attribute loses importance in case of comorbidity.

‡A *P* value less than or equal to .05 was regarded as significant.

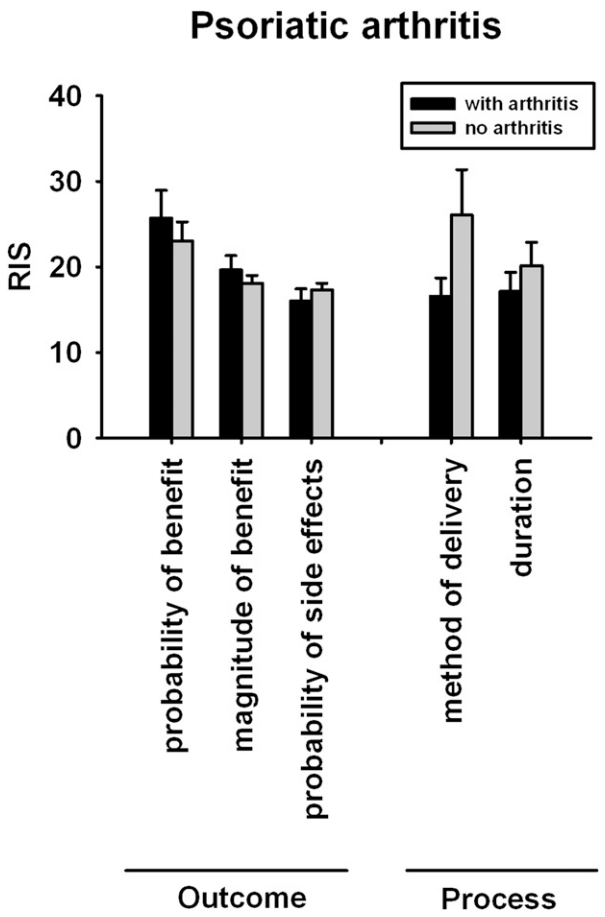

Fig 1. Treatment preferences of participants with psoriatic arthritis compared with those without arthritis. No significant differences in relative importance scores (RIS) were noted with ANOVA tests. *Bars*: Standard error of the mean (SEM).

severity (RIS = 14.97), and side-effect reversibility (RIS = 15.62) were considered less important.[26]

The impact of comorbidities on treatment preferences was determined by descriptive comparison and in multivariate logistic regression models controlling for age, sex, PASI, and DLQI. Analyses were performed for all outcome and process attributes, but only attributes with significant differences in RIS are shown (Figs 1-3, Table IV).

No significant difference was observed in descriptive comparison of participants with and without psoriatic arthritis, although there was a trend for participants with arthritis to care less about the delivery method (see Fig 1). However, regression models indicated that participants with psoriatic arthritis consider the probability of benefit as significantly more important than those without arthritis (β = 0.166, P = .037; see Table IV).

In patients with diabetes, a tendency to care less about the probability of benefit and the delivery method was noted, but differences did not reach significance (Fig 2, *A*). Patients reporting a history of cardiovascular disease were significantly less concerned about the magnitude of benefit (RIS = 13.66 vs 19.24, P = .02; Fig 2, *B*), but more concerned about the probability of side effects (β = 0.179, P = .046 in regression models; Table III).

Interestingly, treatment preferences were substantially influenced by depression (Fig 3, Table IV). Participants suffering from depression attached less importance to the magnitude of benefit than those without depression (RIS 13.26 vs 19.26, P = .014 in ANOVA, Fig 3; β = −0.196, P = .017 in regression models, Table IV). However, they attached more importance to treatment duration (β = 0.163, P = .047) and individual cost (RIS 21.78 vs 16.98, P = .023; data not shown).

DISCUSSION

Although psoriasis is associated with enormous physical and psychological burden, adherence to

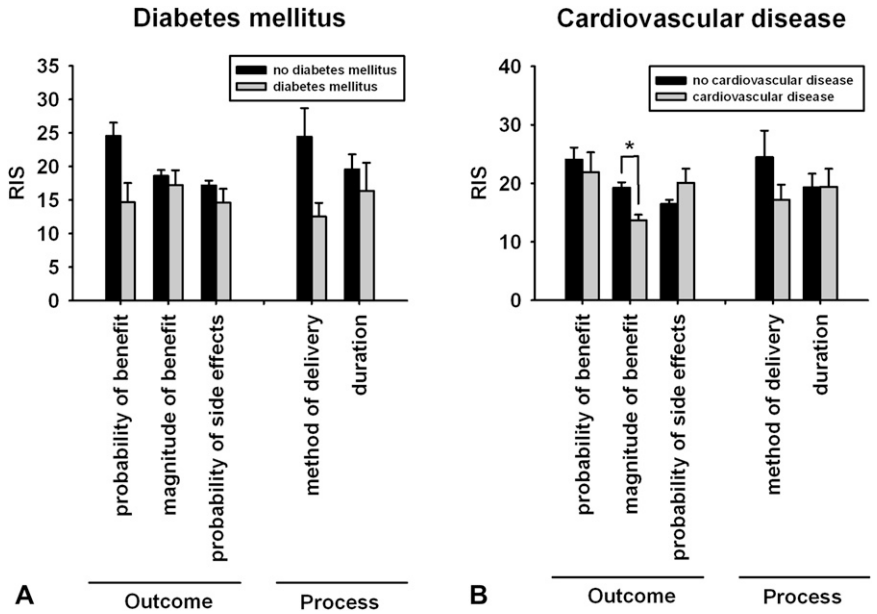

Fig 2. Impact of diabetes and cardiovascular disease on treatment preferences. No significant differences were found with respect to diabetes (**A**). However, participants with cardiovascular disease were found to place less importance on the magnitude of benefit as compared with others (RIS = 13.66 vs 19.24, $P = .02$) (**B**). Differences between relative importance scores (RIS) were tested for statistical significance with ANOVA. *Bars*: Standard error of the mean (SEM). *Asterisk*, $P < .05$.

prescribed treatments is often poor.[17] Up to half of the prescriptions issued for psoriasis treatment are never redeemed.[31] Reasons for poor adherence include frustration with low effectiveness of the prescribed treatment, inconvenience of application, and fear of or actual occurrence of side effects.[32] Several factors can contribute to improve self-management of patients with psoriasis: (1) an effective doctor-patient relationship in which patients' preferences and life circumstances are integrated into shared decision-making; (2) individualized counseling and education; (3) optimism with the treatment prescribed; and (4) limited nuisance in terms of side effects and application mode.[17,33,34] Indeed, treatment adherence improves when individual preferences are taken into consideration.[35]

Herein we show that comorbidities significantly impact participants' preferences for psoriasis treatments. Patients with psoriatic arthritis attached more importance to the probability of benefit than those without arthritis. Psoriatic arthritis has considerable detrimental effect on individuals' health-related quality of life, affecting physical activity, but also mental and social well-being and work ability.[36,37] In a recent willingness-to-pay analysis, patients with psoriatic arthritis appeared willing to pay large amounts to eliminate symptoms.[38] Issues regarded as especially precious were physical comfort, emotional health, sleep, and work. As a result, the desire to find an appropriate treatment is especially large for patients with psoriatic arthritis, and physicians should not hesitate to escalate therapy if symptoms are not properly controlled.[39]

In the whole study collective, side effect–related attributes were regarded as less important than the probability and magnitude of benefit, suggesting that participants were prepared to trade side effects for better therapeutic outcome (for discussion, see Schaarschmidt et al[26]). However, patients suffering from cardiovascular disease cared less about the magnitude of benefit and more about the probability of side effects. Indeed, these patients are at higher risk of adverse effects when receiving systemic antipsoriatic therapy.[40,41] For example, treatment with acitretin may lead to hyperlipidemia; cyclosporine may evoke hypertension and renal insufficiency; and tumor necrosis factor–α antagonists may worsen cardiac insufficiency. If prescribing systemic antipsoriatic medications for patients with cardiovascular disease, physicians should carefully address patients' concern and fear of side effects. Some patients may have experienced life-threatening cardiovascular events and, as a consequence, their major concern may be to avoid additional risk.

Notably, study participants with depression viewed the magnitude of benefit as less important compared with other study participants. This

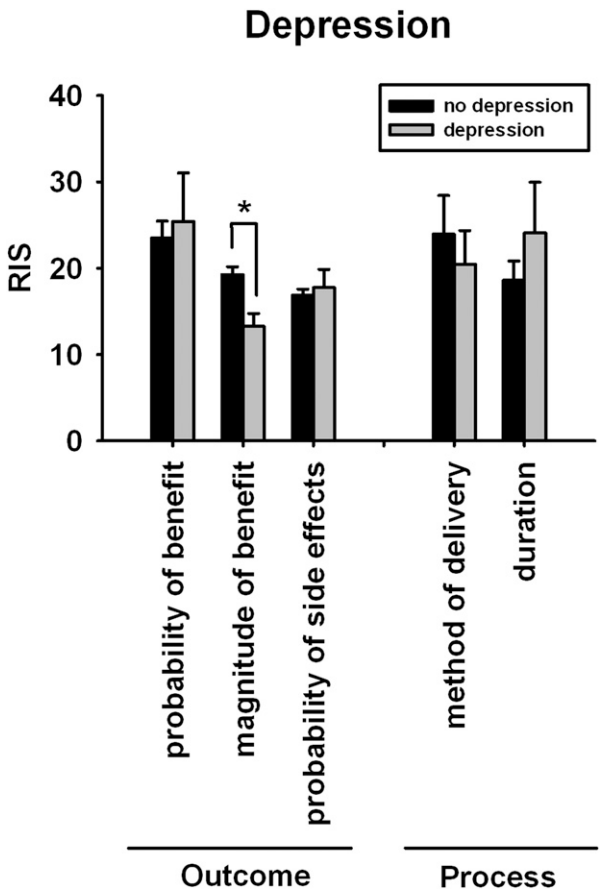

Fig 3. Patients with psoriasis suffering from depression place less importance on magnitude of benefit as compared with others (RIS = 13.26 vs 19.26, P = .014). Differences between relative importance scores (RIS) were tested for statistical significance with ANOVA. *Bars*: Standard error of the mean (SEM). *Asterisk*, $P < .05$.

indifference toward improving their skin condition involves a high risk of non-adherence. Indeed, patients with depression are less compliant with the use of antipsoriatic medication and use health care service less frequently.[42-44] High rate of noncompliance with therapy among depressed individuals is also a well-known problem in other fields of medicine, for example, in diabetology and cardiology.[45,46] In a potentially vicious cycle, noncompliance can result in deteriorated treatment outcome, which might trigger or worsen depression.

Participants with depression, compared with others, attached more importance to treatment duration. Therefore time consuming treatments may not be feasible in cases of depression, where loss of energy and fatigue are frequently encountered. Moreover, participants self-reporting depression were more concerned about individual cost. Indeed, depression has detrimental impact on working ability, employment, and socioeconomic status. According to a recent meta-analysis, 35% to 50% of employees with depression take short-term disability leave from work, and their annual income is reduced by approximately 10% when compared with unaffected employees.[47] Individuals with depression are also at increased risk for permanent disability.[48] However, according to data from the German Federal Office for statistics, the number of lost working years is higher for cardiovascular disease than for depression. Therefore, high concern about cost reported by participants with depression may partly reflect a generally sorrowful attitude. Our preference analysis highlights the importance of assessing the mental health of psoriasis patients because addressing and treating patients' depression may be a currently neglected opportunity to improve care.

Clearly, our findings will have to be verified in larger and more diverse patient samples. It is likely that the significance of certain associations was missed because of the rather small sample size. Moreover, only patients with moderate and severe psoriasis treated in a university hospital were recruited. It remains to be seen whether patients with milder forms of psoriasis, patients treated in other health care facilities, and patients from other countries have similar preferences as the study sample investigated herein.

Compared with other methods of preference assessment, conjoint analysis provides the advantage of realistically reflecting decision-making processes undertaken in daily clinical practice. As such, the method has emerged as a unique tool for capturing insights into patients' preferences for treatment processes and outcomes. It is hoped that results of our and other analyses will contribute to optimizing shared decision-making, treatment adherence and satisfaction, and, ultimately, therapeutic efficiency.

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