

# Therapeutic approaches in psoriasis: a post-hoc analysis of the PSYCHAE study from a gender point of view

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## Summary

**PSYCHAE was a multicenter observational study conducted in 2004-2005, which included 1580 psoriatic patients. We performed a post-hoc analysis to explore gender differences and the gender-specific therapeutic approaches adopted by Italian dermatologists. Type, severity and duration of psoriasis, presence of psoriatic arthritis, General Health Questionnaire score, Brief COPE questionnaire, Brief Symptom Inventory indexes and prescribed therapies were compared between genders.**

**786 patients were evaluable for the analysis, 477 (61%) males. Highly significant differences were found in frequency of alcohol consumption and of smokers, which were higher in men, and in GHQ-12 and all BSI scores, which were all significantly worse in women at baseline. Other significant differences were familiarity for psoriasis or arthritis (higher in women), and severity of psoriasis (higher in men). Topical pharmacological therapy was the most prescribed treatment in both genders and no significant differences were observed in**

**prescribed therapies, except for phototherapy (37% of males vs 29% of females;  $p=0.0121$ ).**

**With the major limitation of referring to a cohort studied in 2004-2005, when biologicals were not used yet for psoriasis, this analysis shows that, at that time, Italian dermatologists seemed to have the same approach in treating male and female patients with psoriasis, although females should have deserved more attention to their higher psychological distress.**

*KEY WORDS: psoriasis; gender; therapy; PSYCHAE.*

## Background

It is now clear that sex and gender affect prevention, clinical signs, therapeutic approach, prognosis and psychological features (1). Studies have shown that there are gender differences with regard to disease characteristics in immune-mediated inflammatory diseases, including rheumatoid arthritis, inflammatory bowel diseases, and psoriasis (2).

The PSYCHAE study is a multicenter Italian study conducted in 2004 on 1580 patients with psoriasis, in order to evaluate the prevalence and incidence of psychopathological distress, to establish whether psoriasis severity and psychopathological distress are associated in these patients and the strategies to cope with the disease adopted by both dermatologists and patient themselves (3). The results pointed out that the psychological status of women was worse than that of men independently from the severity of psoriasis. However, the therapeutic approaches were not analyzed from a gender point of view. Since then, many differences have been reported between genders in psoriatic patients, in terms of epidemiology (4), pattern and burden of disease (5), search for care (6), and choice of therapy (7, 8). Thus, the large cohort of patients provided by the PSYCHAE study database offered a great opportunity to explore the gender-specific therapeutic approaches adopted by the 39 Italian dermatologic centers participating in the study.

This short paper reports the between gender comparisons in the prescribed treatment for psoriasis at baseline and follow up visits in patients enrolled in the PSYCHAE study.

## Methods

PSYCHAE was a multicenter observational study, conducted in 39 dermatology clinics widely distributed

throughout Italy, aimed to define the prevalence and incidence of psychopathological distress in a large sample of Italian patients with psoriasis, and to identify the strategies employed by dermatologists to take care of such patients. The PSYCHAE study included 1580 consecutively enrolled patients with psoriasis aged between 18 and 65 years. Details about methods and results of the study are reported elsewhere (3).

Patients of the PSYCHAE study were considered evaluable for this post-hoc analysis provided that gender was specified and baseline and all follow up visits data were available. Combined treatments i.e. methotrexate+cyclosporine (or retinoids), cyclosporine+retinoids, phototherapy+methotrexate (or cyclosporine) were prescribed in a small number of patients (<3% of evaluable patients), thus it was decided to maintain those patients in the analysis. Patients with missing data in selected parameters were not evaluated for those parameters.

In this analysis, the following variables were compared between genders:

- age
- demographic characteristics
- type, severity and duration of psoriasis
- presence of psoriatic arthritis
- General Health Questionnaire (GHQ-12), which was used to evaluate minor psychological distress (9, 10)
- Brief Symptom Inventory (BSI), which was used to evaluate major psychological distress (11), including: total BSI, Global Stress Index (GSI), Positive Symptom Total (PST), Positive Symptom Distress Index (PSDI), T-GSI (GSI transformed into a T-score using age-specific reference values, calculated as  $[(\text{Subject GSI} - \text{mean GSI})/\text{SD GSI}] + 50$ ; a value of T-GSI > 63 is considered to indicate major psychological disease
- prescribed therapies, classified as phototherapy (including PUVA, UVA, UVB, TL01 and other), topical pharmacological therapy (including keratolytics, vitamin D3-derivatives, tazarotene, steroids, moisturizers or other), systemic pharmacological therapy (including methotrexate, cyclosporine, retinoids and other), other non-pharmacological treatments (including diet, smoke avoidance, heliotherapy, thermal care and other)
- adverse events occurred during study.

Moreover, GHQ-12 and T-GSI scores were compared between menopausal females and  $\geq 50$ -year-old males patients, pre-menopausal females and <50-year-old males and according to level of education. For level of education the following classes were considered: low (none or primary school), medium (middle school) and high (senior high school or academic degree).

All analyses were performed with SAS v. 9.2 and Enterprise Guide 4.3. Comparisons were performed by Student T-test, Chi-square test or Fisher's exact test if appropriate. The accepted level of significance was set at  $\alpha=0.05$ .

## Results

Overall, 786 patients out of the 1580 of the PSYCHAE study were evaluable for this post-hoc analysis, 477 (61%) males. Among the 309 female patients, the menopausal status was available for 282 women; 40% of them were in menopausal status.

The comparisons between demographic and disease characteristics of male and female patient populations are reported in Table 1. Men and women were well matched for age and educational level but they significantly differ for alcohol consumption and smoke at baseline: 76% of male vs 49% of female patients had alcohol consumption and 44% of males vs 35% of females were smokers at baseline (Chi-Square test  $p$ -value<0.001 for both variables). Moreover, significant differences were detected for familiarity for psoriasis or arthritis (48% of females vs 39% of males; Chi-Square test  $p$ -value=0.0168), type of psoriasis (90% of females vs 94% of males had vulgaris and 5% of males vs 2% of females had pustulosa psoriasis; Fisher Exact test  $p$ -value=0.03662) and severity of psoriasis (mean BSA was 29.9% for females vs 35.4% for males; T-test  $p$ -value=0.00247).

Table 2 summarizes the baseline values concerning psychological evaluations compared between genders: despite the major severity of diseases in men than in women, the major and minor psychological distress measured with BSI and GHQ-12 were significantly worse in the female population. Moreover, significant differences between menopausal females vs  $\geq 50$ -year-old males and pre-menopausal females vs <50-year-old males at baseline in GHQ-12 and T-GSI scores were maintained (Table 3). Significant differences were also observed in high vs low educational level patients: the mean (SD) GHQ-12 score was 2.6 (3.2) vs 3.3 (3.1) (T-test,  $p$ -value = 0.0166) and the mean (SD) T-GSI score was 48.2 (9.4) vs 50.2 (9.4) (T-test,  $p$ -value = 0.0470). Furthermore, significant differences for T-GSI score were detected in high vs medium educational level patients (48.2 (9.4) vs 50.4 (10.1); T-test,  $p$ -value = 0.0156) indicating the importance of minor and major psychosocial aspects.

Concerning prescribed therapies, no significant differences were observed in the class of treatment neither at baseline nor at follow up visits except for phototherapy at baseline (37% of males vs 29% of females; Chi-square test  $p$ -value=0.0121) (Table 4).

Adverse events during study were reported in 10 patients (1.3% of evaluable), 3 females and 7 males.

## Discussion

Study male and female patient cohorts were rather homogeneous for demographic and disease characteristics, but differed significantly for smoking that is an independent risk factor for psoriasis (12) and drinking habits. The association between alcohol consumption and psoriasis has been greatly discussed and a systematic review affirms that alcohol consumption was

Table 1 - Demography and psoriasis characteristics in male and female study patients at baseline.

Variable	Males	Females	p-value
<b>Age (years), mean (SD)</b>	45.3 (12.1)	43.7 (13.0)	0.08537
<b>Education (n, %<sup>^</sup>)</b>			0.1158
None	4 (1.3)	2 (0.4)	
Primary school	64 (20.9)	92 (19.3)	
Middle school	78 (25.5)	155 (32.5)	
Senior high school	125 (40.8)	189 (39.6)	
Academic degree	35 (11.4)	39 (8.2)	
<b>Alcohol consumption (n, %<sup>^</sup>)</b>	363 (76.1)	150 (48.7)	<0.0001
<b>Smokers (n, %<sup>^</sup>)</b>	210 (44.1)	107 (34.6)	<0.0001
<b>Concomitant or previous diseases (n, %<sup>^</sup>)</b>	199 (42.1)	135 (44.1)	0.5902
<b>Previous surgery (n, %<sup>^</sup>)</b>	219 (46.2)	163 (52.9)	0.0662
<b>Familiarity for psoriasis or arthritis (n, %<sup>^</sup>)</b>	177 (38.6)	140 (47.5)	0.0168
<b>Presence of psoriatic arthritis (n, %<sup>^</sup>)</b>	105 (22.3)	59 (19.4)	0.3296
<b>Type of psoriasis (n, %<sup>^</sup>)</b>			0.03662
Vulgaris- Pustolosa	5 (1.6)	7 (1.5)	
Vulgaris- Inversa	6 (1.9)	9 (1.9)	
Vulgaris- Eritrodermic- Pustolosa	1 (0.3)	0 (0)	
Vulgaris- Eritrodermic	0 (0)	4 (0.8)	
Vulgaris	278 (90.3)	446 (93.7)	
Pustolosa	15 (4.9)	7 (1.5)	
Inversa	1 (0.3)	0 (0)	
Eritrodermic	2 (0.6)	3 (0.6)	
<b>Type of arthritis (n, %<sup>*</sup>)</b>			0.93265
Axial	4 (6.9)	5 (4.9)	
Peripheral-polyarticular	19 (32.8)	36 (34.9)	
Peripheral-oligoarticular	34 (58.6)	59 (57.3)	
Other	1 (1.7)	3 (2.9)	
<b>Severity of psoriasis, BSA (%) mean (SD)</b>	35.4 (25.3)	29.9 (22.6)	0.00247
<b>Duration of disease, (years) mean (SD)</b>	14.7 (10.6)	14.7 (12.7)	0.98199

<sup>^</sup> Percentages calculated over the total number of evaluable patients without missing data.

<sup>\*</sup> Percentages calculated over total number of evaluable patients with presence of psoriatic arthritis and with available type of arthritis.

more prevalent in psoriasis patients. In fact, psoriasis patients consumed more alcohol than the controls. However, there is not enough evidence to establish whether alcohol consumption is indeed a risk factor for psoriasis (13). The major smoking and alcohol attitude in male vs female patients mirrors the situation in the general population, where smoke and alcohol consumption, though growing in women, is still higher among men.

Concerning clinical presentation of psoriasis, it has been reported in previous works that psoriatic arthritis is more frequent in men than in women, particularly in

its axial presentations (14), while females are more likely to have peripheral joint involvement (15). The explanation for these differences is not clear, however these clinical expression trends in men and women with arthritis persisted in a more recently published series, which confirmed the greater peripheral involvement in women with psoriatic arthritis (with more frequent polyarthritis), as well as greater physical functional impairment (16). In our series, conversely, no significant difference was observed in prevalence of psoriatic arthritis in male and female patients. Moreover, a recent study by Hagg et al. (17) found that men

Table 2 - Mean baseline General Health Questionnaire (GHQ-12) score and Brief Symptom Inventory (BSI) indexes in males and females.

Variable	Males	Females	p-value
<b>GHQ-12 score</b>			
Mean (SD)	2.5 (3.0)	3.5 (3.2)	<0.0001
> 3 (%)	30.3	43.2	0.0003
<b>BSI scores</b>			
Total BSI [Mean (SD)]	23.2 (21.8)	32.1 (26.6)	<0.0001
GSI [Mean (SD)]	0.4 (0.4)	0.6 (0.5)	<0.0001
PST [Mean (SD)]	16.6 (11.7)	20.6 (12.3)	<0.0001
PSDI [Mean (SD)]	1.2 (0.4)	1.4 (0.5)	<0.0001
T-GSI [Mean (SD)]	47.9 (8.7)	51.4 (10.6)	<0.0001
T-GSI >63 (%)	6.9	16.4	0.0001

GHQ-12: 12 items General Health Questionnaire; BSI: Brief Symptom Inventory; GSI: Global Stress Index; PST: Positive Symptom Total; PSDI: Positive Symptom Distress Index; T-GSI: T-score GSI

Table 3 - GHQ-12 and T-GSI scores at Baseline in menopausal and pre-menopausal females compared to age-comparable males.

	GHQ-12 score Mean (SD)	T-test p-value	T-GSI score Mean (SD)	T-test p-value
<b>Menopausal females</b>	3.7 (3.2)	0.0008	52.9 (11.2)	0.001
<b>≥ 50-year-old males</b>	2.4 (2.8)		48.4 (7.8)	
<b>Pre-menopausal females</b>	3.4 (3.3)	0.0049	50.6 (10.1)	0.0024
<b>&lt;50-year-old males</b>	2.5 (3.1)		47.5 (9.2)	

GHQ-12: 12 items General Health Questionnaire; GSI: Global Stress Index; T-GSI: T-score GSI

had a more severe psoriasis than women, consistent across all age groups and at different follow-up times, and further that men tended to have higher PASI values compared to women. In our cohort, the severity of disease, as measured by percentage of body surface area (BSA) involved, was slightly higher in men than in women (35.4% vs 29.9%, T-test p-value=0.002).

The quality of life (QoL) of patients with psoriasis is markedly impaired by chronic skin lesions and their negative body image due to the presence of the skin lesions and that is why the importance of patient-generated evaluations in assessing the impact of health-care has been widely recognized in recent years (18, 19). In our sub-analysis, as already pointed out by the PSYCHAE study (3), the General Health Questionnaire and all the BSI scores were significantly higher in females than in males, indicating a higher psy-

chosocial distress among women at baseline. Other authors had previously reported that female patients with psoriasis had greater impact scores in QoL questionnaires (20), especially for the symptoms and feelings domain (21). These findings could be explained by the general female stereotype that shows greater interest in appearance and a greater dependency on social relationships than male. Therefore, these findings suggest that QoL and psychological impact assessment play a greater role in females than in the males, when assessing the severity of psoriasis. Looking more in detail to both males and females scores, all progressively decrease at follow up visits (data not shown), which could be explained by the well described effect on perceived wellbeing of entering a clinical study and being regularly followed up. The PSYCHAE study had already reported that minor

Table 4 - Treatment prescribed for psoriasis in male and female study patients at each visit.

Type of therapy	Males (n, %)	Females (n, %)	Chi-square Test; p-value
<b>Topical pharmacological therapy</b>			
Baseline	357 (74.8)	224 (72.5)	0.6462
3 months	330 (69.2)	227 (73.5)	0.2715
6 months	330 (69.2)	226 (73.1)	0.2017
12 months	340 (71.3)	228 (73.8)	0.4103
<b>Systemic pharmacological therapy</b>			
Baseline	192 (40.3)	111 (35.9)	0.2188
3 months	181 (37.9)	100 (32.4)	0.0903
6 months	161 (33.8)	88 (28.5)	0.1252
12 months	125 (26.2)	66 (21.4)	0.1103
<b>Phototherapy</b>			
Baseline	178 (37.3)	88 (28.5)	0.0121
3 months	75 (15.7)	46 (14.9)	0.7281
6 months	82 (17.2)	42 (13.6)	0.1784
12 months	73 (15.3)	34 (11.0)	0.0809
<b>Other non-pharmacological therapies</b>			
Baseline	131 (27.5)	83 (26.9)	0.9682
3 months	125 (26.2)	72 (23.3)	0.3459
6 months	86 (18.0)	46 (14.9)	0.2551
12 months	138 (28.9)	100 (32.4)	0.3102

psychological distress, present in 46% of patients at enrolment, halved during the study (22). Menopausal status seems not to affect psychological distress among women, while significant differences between genders at baseline are maintained. Interestingly, on the other hand, highly educated patients suffer less from disease-associated reduction in well-being and distress than low educated.

Coming to the treatment approaches, it has to be necessarily taken into account that the PSYCHAE study was carried out in 2004-2005, when biological drugs were not used yet for the treatment of psoriasis, so they were not considered. Topical therapy was the most prescribed in both men and women, followed by systemic therapy (Table 4), mainly cyclosporine (data not shown). Previous studies indicated that men receive systemic or UV treatment for psoriasis in greater extent than women (23, 24). Also in the PSYCHAE patients, phototherapy had been slightly more prescribed in men than in women, at least at baseline. There was no other difference between sexes in the therapeutic approach adopted by Italian dermatologists to care for psoriasis. Actually, there is a great challenge for dermatologists to pay greater attention to the psychological distress that these patients experience. The outcome of QoL and psychological measurements should be taken into account when deciding on treatment strategies, since optimal therapy can only be achieved by addressing both the physical and psychosocial effects of the disease. The choice of the optimal psoriasis treatment should also take into account the effect of the drug on the patient's psychosocial well-being, and adjunctive psychological interventions before and during treatment could be of benefit especially for women. The results of the PSYCHAE study had shown that dermatologists appear much

more interested in investigating the superficial skin rather than the deep emotions of their patients. The PSYCHAE results also revealed, by means of the Brief COPE questionnaire, that almost all study physicians showed a problem-orientated coping style and that coping was a predictor of disease evolution (3, 22). Actually, they show, through this specific sub-analysis, adopting the same therapeutic approach for males and females, despite the higher major and minor psychological distress experienced by the latter. Instead, it is recommended that psoriasis patients, especially women with severe disease, receive a more holistic, multitarget approach that encompasses both medical and psychological measures. There is need to provide psychological assistance to female patients with psoriasis followed at dermatology centers. Therapeutic options could include cognitive-behavioral therapy and emotional disclosure (25,26).

This paper has the major limitation that it refers to data collected between 2004 and 2005, when no biological drugs were available for psoriasis, so our analysis lacks information about this important treatment for moderate to severe psoriasis. For example, there is an active discussion ongoing on whether women are discriminated by not receiving the same quantity of high-priced drugs as men in several fields of medicine (7, 27).

On the other hand, we thought that the PSYCHAE database represented a great opportunity, with its wide cohort of psoriatic patients, to preliminary explore the gender-specific therapeutic approach to psoriasis by Italian dermatologists.

It can be concluded that, at least in 2005, dermatologists in Italy seemed to have the same approach in treating male and female patients with psoriasis, although females might have deserved more attention

to their psychological distress, which was higher than in men, and possibly a multitarget intervention. A new specifically designed study could be of interest to investigate if something has changed toward a more gender-specific therapeutic attitude in recent years, also considering the entry of biologicals in the treatment armamentarium for psoriasis.

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### Conflict of Interests

D.C. is a part-time employee of Novartis Farma Italy and received grants from Allergan and Aventis.

S.C. has received advisory/speaker honoraria and/or research funding from Abbvie, MSD, Novartis and Pfizer

A.G. No conflict of interest

A.C. No conflict of interest

F.F. No conflict of interest

S.R. is an employee of Medidata srl

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### Appendix

List of participating centers:

Tor Vergata University of Rome (Chimenti, Bianchi); University of Padova (Veller, Gallo); University of Naples Federico II (Santojanni, Baldo); University of Siena (Andreassi, Flori); University of Brescia - Azienda Spedali Civili (Calzavara Pintón, Zane); University of Parma (De Panfilis, Di Nuzzo); University of Milan (Finzi, Cattaneo); University of Ferrara (Virgili, Altieri); II University of Naples (Ruocco, Lo Schiavo); University of Trieste (Trevisan, Kokelj); University of Chieti (Tullí, Masci); University of Milan (Caputo, Locatelli); University of Bologna (Varotti, Bardazzi); University of Modena e Reggio Emilia (Giannetti, Coppini); University of Milan (Marchesi, Reseghetti); University of Florence (Fabbri, Amato); University of Catania (Micali, Lacarrubba); University of Messina (Cannavò, Manfrè); University of L'Aquila (Peris, Cavallaro); University of Torino (Pippione, Soro); University of Verona (Barba, Schena); University of Bari (Angelini, Vena); University of Sassari (Cerimele, Montesu); University of Torino (Bernengo, Bonvicino); University of Cagliari (Biggio, Zueca); Catholic University of Rome (Amerio, Garcovich); University of Palermo (Aricò, Bongiorno); University of Pisa (Barachini, Giuliano); University of Piemonte orientale (Leigheb, Zavattaro); University of Milan (Lodi, Rossini); University of Bari (Rantuccio,

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