Patient experience of depression and alexithymia

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Limiting psoriasis to a skin problem is a rather restrictive approach

The SKIN-EGO, Didier Anzieu

The functions of the skin-ego are to maintain thoughts, to contain ideas and affects, to provide a protective shield, to register traces of primary communication with the outside world, to manage intersensorial correspondences…..

In brief, the skin-ego is an interface between inside and outside, and is the foundation of the container/contained relationship.
Beyond the patch there is a person
Beyond the patch there is a person

Beyond a person, there is the world
PSORIASIS

Effect on self-image, self-esteem, well-being…

Psychological problems ↔ Social problems
Psychological problems

Anxiety, depression, lack of self-confidence, resignation, helplessness...

Avoidance of situations

Stress

Social problems

Stigmatization, social phobia

Work, family, sexual relations

A vicious circle
Psychological problems
Anxiety, depression, lack of self-confidence, resignation, helplessness…
Avoidance of situations

Stigmatization, social phobia
Work, family, sexual relations

Social problems
Stress

Unhealthy behaviors: smoke, alcohol, wrong diet…

A vicious circle
Comorbidities
Psychological problems:
- Anxiety, depression, lack of self-confidence, resignation, helplessness…
- Avoidance of situations

Social problems:
- Stigmatization, social phobia
- Work, family, sexual relations
- Stress

Comorbidities:
- Unhealthy behaviors: smoke, alcohol, wrong diet…

A vicious circle

Exacerbation of clinical aspects
A vicious circle

Psychological problems
- Anxiety, depression, lack of self-confidence, resignation, helplessness...
- Avoidance of situations

Social problems
- Stigmatization, social phobia
- Work, family, sexual relations
- Stress

Comorbidities
- Unhealthy behaviors: smoke, alcohol, wrong diet...

Exacerbation of clinical aspects
THE BURDEN OF PSORIASIS

Psychological problems
- Anxiety, depression, lack of self-confidence, resignation, helplessness...

Social problems
- Stigmatization, social phobia
- Work, family, sexual relations
- Unhealthy behaviors: smoke, alcohol, wrong diet

Avoidance of situations

Stress

Comorbidities

Exacerbation of clinical aspects
THE BURDEN OF PSORIASIS

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Stress

Comorbidities

Exacerbation of clinical aspects

DEPRESSION ON ALEXITHYMIA
Psoriasis and depression
Psoriasis and depression

PubMed search

570 articles

Only title

63 articles
Of 607 patients included, 9.9% (95%CI: 7.5-12.3%) screened positive for major depressive disorder.

Suicidal ideation was reported in 35% of MDD

Risk of MDD was significantly increased in women, those with severe clinical disease, psoriatic arthritis and previous depression/anxiety.
Five thousand Italian patients with psoriasis were mailed the Center for Epidemiological Studies-Depression Scale (CES-D) questionnaire, a 20-item instrument developed to perform epidemiological studies of depressive symptomatology in the general population.

Evaluable questionnaires from 2,391 patients.

Depressive symptomatology was observed in 1,482/2,391 patients (62% overall; females, 63%; males, 61%).
What Is Depression?

Depression (major depressive disorder) is a common and serious medical illness that negatively affects how you feel, the way you think and how you act. Depression causes feelings of sadness and/or a loss of interest in activities once enjoyed. It can lead to a variety of emotional and physical problems and can decrease a person’s ability to function at work and at home.

Depression symptoms can vary from mild to severe and can include:

• Feeling sad or having a depressed mood
• Loss of interest or pleasure in activities once enjoyed
• Changes in appetite — weight loss or gain unrelated to dieting
• Trouble sleeping or sleeping too much
• Loss of energy or increased fatigue
• Increase in restless activity (e.g., hand-wringing or pacing) or slowed movements and speech
• Feeling worthless or guilty
• Difficulty thinking, concentrating or making decisions
• Thoughts of death or suicide

Symptoms must last at least two weeks for a diagnosis of depression.

Depression affects an estimated one in 15 adults (6.7%) in any given year.
Instruments for assessing depression

- Beck Depression Inventory (BDI)
- Hospital Anxiety and Depression Scale (HADS)
- Hamilton Rating Scale for Depression (HAM-D)
- Patient Health Questionnaire (PHQ-9)
- Quick Inventory of Depressive Symptomatology (QIDS)
- Montgomery-Asberg Depression Rating Scale (MADRS)
- The Quick Inventory of Depressive Symptoms (QIDS)
- ...

A useful depression scale should contain the following features:

- Brief;
- Acceptable to patients;
- Covers all DSM-IV diagnostic criteria for major depressive disorder;
- Reliable (internal consistency and test-retest reliability);
- Convergent validity (correlates with other measures of depression);
- Discriminant validity (correlates lower with measures of other symptom domains, such as anxiety);
- Indicator of symptom severity;
- Indicator of remission status;
- Case-finding capability as a screening instrument;
- Assesses psychosocial function;
- Assesses quality of life;
- Assesses suicidal thoughts;
- Sensitive to change;
- Easy to score;
- Inexpensive.
<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>INSTRUMENT</th>
<th>PREVALENCE OF DEPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamb RC et al. Br J Dermatol 2016</td>
<td>PHQ-9</td>
<td>9.9%</td>
</tr>
<tr>
<td>Tee SI et al. J Eur Acad Dermatol Venereol 2016</td>
<td>HADS</td>
<td>15%</td>
</tr>
<tr>
<td>Cohen BE et al. JAMA Dermatol 2016</td>
<td>PHQ-9</td>
<td>16.5%</td>
</tr>
<tr>
<td>Cohen BE et al. JAMA Dermatol 2016</td>
<td>HADS</td>
<td>24%</td>
</tr>
<tr>
<td>Dalgard FJ et al. J Invest Dermatol 2015</td>
<td>HADS</td>
<td>13.8%</td>
</tr>
<tr>
<td>Karia SB et al. Ind Psychiatry J 2015</td>
<td>HAM-D</td>
<td>18%</td>
</tr>
<tr>
<td>AlShawan MA et al. J Cutan Med Surg 2015</td>
<td>HADS</td>
<td>14%</td>
</tr>
<tr>
<td>Korkoliakou P et al. Ann Gen Psychiatry 2014</td>
<td>BDI</td>
<td>67%</td>
</tr>
<tr>
<td>Esposito M et al. Dermatology 2006</td>
<td>CES-D</td>
<td>62%</td>
</tr>
</tbody>
</table>
Table 3. Depression in patients with common skin diseases and controls in percentages and ORs (95% confidence interval) \( N = 4,994 \)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Depression clinical case HADS ( \geq 11 % ) (( n ))</th>
<th>( P )-value</th>
<th>Crude OR(^1) depression clinical case HADS &gt; 11</th>
<th>Adjusted OR(^2) depression clinical case HADS &gt; 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>13.8 (84)</td>
<td>&lt;0.001</td>
<td>3.23 (2.06–5.05)</td>
<td>3.02 (1.86–4.90)</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>4.8 (18)</td>
<td>0.729</td>
<td>1.21 (0.62–2.36)</td>
<td>0.97 (0.41–2.32)</td>
</tr>
<tr>
<td>Infections skin</td>
<td>8.9 (21)</td>
<td>0.001</td>
<td>2.59 (1.40–4.76)</td>
<td>2.65 (1.39–5.06)</td>
</tr>
<tr>
<td>Eczema</td>
<td>8.0 (18)</td>
<td>0.007</td>
<td>1.79 (0.89–3.59)</td>
<td>1.68 (0.80–3.53)</td>
</tr>
<tr>
<td>Acne</td>
<td>5.7 (12)</td>
<td>0.311</td>
<td>1.53 (0.74–3.13)</td>
<td>1.74 (0.73–4.17)</td>
</tr>
<tr>
<td>Nevii</td>
<td>6.0 (11)</td>
<td>0.215</td>
<td>2.05 (0.99–4.22)</td>
<td>2.14 (1.01–4.53)</td>
</tr>
<tr>
<td>Atopic eczema</td>
<td>10.1 (16)</td>
<td>&lt;0.001</td>
<td>3.55 (1.82–6.92)</td>
<td>3.27 (1.61–6.62)</td>
</tr>
<tr>
<td>Benign skin tumors</td>
<td>4.8 (7)</td>
<td>0.587</td>
<td>1.50 (0.69–3.65)</td>
<td>1.43 (0.55–3.74)</td>
</tr>
<tr>
<td>Hand eczema</td>
<td>15.1 (21)</td>
<td>&lt;0.001</td>
<td>4.85 (2.59–9.10)</td>
<td>4.00 (2.01–7.97)</td>
</tr>
<tr>
<td>Leg ulcers</td>
<td>24.3 (28)</td>
<td>&lt;0.001</td>
<td>11.23 (5.71–22.09)</td>
<td>10.17 (4.07–25.41)</td>
</tr>
<tr>
<td>Dermatological out-patients overall</td>
<td>10.1 (357)</td>
<td>&lt;0.001</td>
<td>2.69 (1.88–3.84)</td>
<td>2.40 (1.67–3.47)</td>
</tr>
<tr>
<td>Controls</td>
<td>4.3 (58)</td>
<td>—</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Measure of the impact of psoriasis on quality of life using the SF-36

Figure 1. Quality of life in psoriasis - Comparison with SF-36 norms: minor medical conditions, severe medical conditions, psychiatric conditions.
12-item General Health Questionnaire (GHQ-12)

• Detection of the possible presence of minor non psychotic psychiatric disorders (anxiety and depression)
• Scores 0 0 1 1
• GHQ case when the score is 4 or more.
<table>
<thead>
<tr>
<th>Severity</th>
<th>N tot</th>
<th>% GHQ+</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>very mild</td>
<td>93</td>
<td>34.4</td>
<td>25.1 – 45.1</td>
</tr>
<tr>
<td>mild</td>
<td>335</td>
<td>44.8</td>
<td>39.4 – 50.3</td>
</tr>
<tr>
<td>moderate</td>
<td>276</td>
<td>50.4</td>
<td>44.3 – 56.4</td>
</tr>
<tr>
<td>severe/very severe</td>
<td>207</td>
<td>58.9</td>
<td>51.9 – 65.6</td>
</tr>
</tbody>
</table>
This study examined the risk of **new-onset depression** in patients with psoriasis in a nationwide Danish cohort including some 5 million people in the period 2001-2011.

A total of 35,001 patients with mild psoriasis and 7,510 with severe psoriasis were identified.

Incidence rates for depression were 20.0 (95% confidence interval 19.9-20.0), **23.9** (23.1-24.7) and **31.6** (29.5-33.8) for the reference population, mild, and severe psoriasis, respectively.

Adjusted for age, sex, and inclusion year, IRRs were 1.08 (1.04-1.12) in mild and 1.36 (1.27-1.46) in severe psoriasis.

In conclusion, the risk of new-onset depression in psoriasis is mediated primarily by comorbidities, except in younger individuals with severe psoriasis, in whom psoriasis itself may be a risk factor.
Psychological sequelae can be studied also using qualitative methods


- Semi-structured interviews and thematic analysis.
- The principle study finding was that psychological morbidity in psoriasis is considerable. Though mood and anxiety symptoms were present in participants, and were occasionally severe, more prominent sequelae of psoriasis were embarrassment, shame, impaired self-image, low self-esteem, self-consciousness and stigmatisation.
- The perception of psoriasis as an incurable disease beyond respondents' control, with consequent pessimism regarding prognosis and treatment efficacy, was a contributor to psychological morbidity.
- Our conclusion is that the psychological effects of psoriasis can be considerable and long-lasting and are evident across a broad range of psoriasis severities. Clinicians should be aware that psychological sequelae are complex and encompass a range of psychological morbidities beyond conventional psychiatric diagnoses.
Psoriasis and alexithymia
The term was introduced by Sifneos, deriving it from the Greek "alexis" (no words) and "thymos" (emotion), based on the observation that patients with some medical conditions that may be associated with psychological comorbidities, such as ulcerative colitis, asthma, peptic ulcer, or rheumatoid arthritis, showed a "marked difficulty in verbally expressing or describing their feelings and an absence or striking diminution of fantasy."
The refined definition of alexithymia includes:

1. Difficulty in identifying feelings and distinguishing between feelings and the bodily sensations of emotional arousal;
2. Difficulty in describing feelings to other people;
3. Constricted imaginative processes, as evidenced by a paucity of fantasies;
4. A stimulus-bound, externally oriented cognitive style, i.e., focusing on describing what is happening in the environment rather than feelings.
The etiology of alexithymia is unclear, and includes genetic aspects, neurobiological deficits, variations in brain organization, insecure attachment with caregivers, and early traumatic experiences.

Alexithymia is considered to act as a triggering factor for a general susceptibility to disease, similarly to depression and anxiety, by exacerbating responses in the autonomic and neuroendocrine system.
• It has been suggested that there may be two types of alexithymia

**Trait alexithymia**

which is a psychological trait that does not change over time

**State alexithymia**

which is state-dependent and may be modified by therapeutic intervention or change in psychological status
Alexithymia and skin conditions

• The association between alexithymia and some dermatological conditions has been previously investigated. No association was found between alexithymia and acne, or seborrheic dermatitis. The association between alexithymia and alopecia areata is controversial.

• Some studies have shown that alexithymia is more prevalent among psoriasis patients than in healthy populations.
• The observed prevalence of alexithymia in patients with psoriasis ranged between 15.6%


• and approximately 33%


In a large and representative Finnish cohort sample, 9.4% of males and 5.2% of females had alexithymia, and in another representative sample of the Finnish population, the prevalence of alexithymia was 9.9%.

In a study on the German general population, 10% of the population exceeded the TAS-20 sum score threshold of 61.
In other studies, there was **no difference** in the prevalence of alexithymia between psoriasis patients and the control group; however, these studies either involved small numbers of patients or the control group included patients with other skin diseases.


How to measure alexithymia

Toronto Alexithymia Scale

5-point Likert scale: 1 = strongly disagree, 2 = neither agree or disagree, 3 = undecided, 4 = agree, 5 = strongly agree.

CUTOFFS:

≤51 = non-alexithymia,
52 – 60 = possible alexithymia
≥61 = alexithymia

3 subscales: difficulty in describing feelings (5 items), difficulty in identifying feelings (7 items), and externally oriented thinking (8 items).
Prevalence of alexithymia in patients with psoriasis and association with disease burden: a multicentre observational study

F. Sampogna¹, L. Puig², P. Spuls³, G. Girolomoni⁴, M.A. Radtke⁵, B. Kirby⁶, M. Brunori⁷, P. Bergmans⁸, P. Smirnov⁹, J. Rundle¹⁰, F. Lavie⁷, C. Paul¹¹

¹Dermatological Hospital IDI-IRCCS, Rome, Italy; ²Universitat Autònoma de Barcelona, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; ³Department of Dermatology, University of Amsterdam, Amsterdam, The Netherlands; ⁴University of Verona, Verona, Italy; ⁵Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; ⁶St Vincent’s University Hospital, Dublin, Ireland; ⁷Janssen-Cilag, Paris, France; ⁸Janssen-Cilag BV, Tilburg, The Netherlands; ⁹Janssen Pharmaceutica NV, Moscow, Russia; ¹⁰Janssen-Cilag Ltd, High Wycombe, Buckinghamshire, United Kingdom; ¹¹Toulouse University and Hôpital Larrey, Toulouse, France

*EPidemiological Study In Patients with Recently Diagnosed PSOriasis
EPIDEPSO Objectives

• EPIDEPSO (NCT01964443): observational, multicentre, prospective, 1-year international study in adult patients with plaque psoriasis (disease duration \( \leq 10 \) years) who are eligible for phototherapy or systemic treatment

• Cross-sectional analysis on baseline data from 670 patients

Primary objective: Prevalence of alexithymia (score \( \geq 61 \) on the 20-item Toronto Alexithymia Scale [TAS-20])

Secondary objectives: Relationship between alexithymia and psoriasis burden

## Methods

- Psoriasis Area and Severity Index (PASI)
- Physician’s Global Assessment (PGA)
- Hospital Anxiety and Depression Scale (HADS)
- Dermatology Life Quality Index (DLQI)
- Alcohol Use Disorders Identification Test (AUDIT)
- Smoking habits
- Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI-PSO)
Overview of baseline characteristics

• A large proportion of patients enrolled had alexithymia:

24.8 % (95% CI: 21.7-28.2)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Total</th>
<th>Alexithymia N=166</th>
<th>No alexithymia N=504</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>392 (58.5)</td>
<td>92 (55.4)</td>
<td>300 (59.5)</td>
<td>0.365</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>278 (41.5)</td>
<td>74 (44.6)</td>
<td>204 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Face/Neck</td>
<td>Yes</td>
<td>279 (41.6)</td>
<td>81 (48.8)</td>
<td>198 (39.3)</td>
<td>0.037</td>
</tr>
<tr>
<td>Hands</td>
<td>Yes</td>
<td>289 (43.1)</td>
<td>95 (57.2)</td>
<td>194 (38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Genitals</td>
<td>Yes</td>
<td>148 (22.1)</td>
<td>32 (19.3)</td>
<td>116 (23.0)</td>
<td>0.334</td>
</tr>
<tr>
<td>Nails</td>
<td>Yes</td>
<td>201 (30.0)</td>
<td>44 (26.5)</td>
<td>157 (31.2)</td>
<td>0.283</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Yes</td>
<td>34 (5.1)</td>
<td>15 (9.0)</td>
<td>19 (3.8)</td>
<td>0.013</td>
</tr>
<tr>
<td>PASI&gt;10</td>
<td>Yes</td>
<td>272 (41.0)</td>
<td>86 (53.1)</td>
<td>186 (37.1)</td>
<td>&lt;0.001</td>
</tr>
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</table>
## Alexithymia vs No alexithymia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Alexithymia N=166</th>
<th>No alexithymia N=504</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>43.7 (16.2)</td>
<td>44.2 (15.3)</td>
<td>43.5 (16.5)</td>
<td>0.450</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7 (5.6)</td>
<td>27.3 (6.3)</td>
<td>26.6 (5.3)</td>
<td>0.402</td>
</tr>
<tr>
<td>Ys. since 1st sympt.</td>
<td>4.6 (3.4)</td>
<td>4.0 (3.0)</td>
<td>4.7 (3.4)</td>
<td>0.160</td>
</tr>
<tr>
<td>PASI</td>
<td>10.4 (7.8)</td>
<td>12.0 (7.7)</td>
<td>9.8 (7.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PGA</td>
<td>2.3 (0.9)</td>
<td>2.3 (0.9)</td>
<td>2.3 (0.9)</td>
<td>0.281</td>
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<tr>
<td>-----------</td>
<td>----------------</td>
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<td>----------------------</td>
<td>---------</td>
</tr>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
<td>Mean (sd)</td>
<td></td>
</tr>
<tr>
<td>DLQI</td>
<td>9.2 (6.9)</td>
<td>13.0 (7.2)</td>
<td>8.0 (6.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HADS-A</td>
<td>7.7 (4.3)</td>
<td>11.0 (3.9)</td>
<td>6.6 (3.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HADS-D</td>
<td>5.3 (4.1)</td>
<td>8.6 (3.9)</td>
<td>4.2 (3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AUDIT score</td>
<td>4.2 (5.3)</td>
<td>6.2 (7.5)</td>
<td>3.6 (4.1)</td>
<td>0.021</td>
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</table>
### Alexithymia vs No alexithymia

<table>
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<tr>
<th>Variable</th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPAI:PSO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absenteeism</td>
<td>7.5 (22.0)</td>
<td>10.7 (26.2)</td>
<td>6.9 (21.0)</td>
<td>0.111</td>
</tr>
<tr>
<td>Presenteeism</td>
<td>18.1 (26.1)</td>
<td>33.3 (31.6)</td>
<td>14.9 (23.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall work productivity loss</td>
<td>21.8 (29.3)</td>
<td>36.1 (33.8)</td>
<td>18.8 (27.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Activity impairment</td>
<td>26.7 (29.5)</td>
<td>41.0 (30.8)</td>
<td>22.0 (27.6)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- **Absenteeism**: Work time missed
- **Presenteeism**: Impairment at work, reduced on-the-job effectiveness
- **Overall work productivity loss**: overall work impairment, absenteeism plus presenteeism
The Box Plots show the descriptive statistics (IQR, mean, median, minimum and maximum) of the probability for alexithymia for each category. The DLQI graph shows the regression line of the regression of the probability for alexithymia against the DLQI score and its 95% CI (light blue area). This graph also shows the 95% Prediction Limits within which the actual probabilities should fall with 95% confidence.
This is the first multicentre study to investigate the prevalence and significance of alexithymia in patients with plaque psoriasis (≤10 years).

A large proportion of the psoriasis patients enrolled had alexithymia (24.8%) and alexithymia was associated with higher psoriasis burden, including significant quality of life impairment, higher levels of anxiety and depression, higher risk of alcohol dependency, and impairment of work productivity.

Interestingly, face/neck and hand psoriatic skin lesions were more prevalent in patients with alexithymia.
EPIDEPSO: Summary and Conclusions

- Detection of alexithymia may be important in clinical practice to identify patients with high psoriasis burden and limited ability to express their feelings
Some final observations...
Hypotheses on the association between psoriasis and alexithymia

The inaccurate self-perception of stress due to alexithymia may lead to **difficulties in coping with stressors**, and ineffective coping may lengthen the exposure to stressors.

In a functional magnetic resonance imaging study, patients with psoriasis had diminished neural and cognitive responses to facial expressions of disgust, probably due to a defect in coping mechanisms.
Does alexithymia change over time or is it a stable personality trait?

- Some studies have shown that alexithymia is stable over time in the general population. This is not the case, however, in individuals with substance use disorders. Moreover, it has been shown that alexithymia may be partly modifiable with therapeutic interventions.

- Probably, a "trait alexithymia" and a "state alexithymia" exist, this latter which may be modified by therapeutic intervention or change in psychological status, and thus of particular interest when studying the relationship between alexithymia and a medical conditions.
It is possible that a chronic condition, such as psoriasis, which has a strong impact on quality of life, may exacerbate alexithymic characteristics.
Conclusions

• Longitudinal studies are needed to assess whether alexithymia represents a lifelong trait in psoriasis, or if it may be influenced by better care (prevention, psychological/social care, treatment) when psoriasis develops.