

The Impact of Systemic Treatment of Atopic Dermatitis on Depressive Symptoms: A Prospective Clinical Cohort Study

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Information on depressive symptoms among patients with atopic dermatitis (AD) undergoing systemic treatment in a real-world setting is scarce. This prospective real-world clinical cohort study analysed data from SwedAD, a Swedish national register comprising patients with AD undergoing systemic treatment. Data were collected at baseline ($n = 120$) and at follow-up at 6 months (range 3–9 months, $n = 59$), and 12 months (10 months or later, $n = 36$). Depression was assessed with the Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S) and AD with the Eczema Area Severity Index, the Patient-Oriented Eczema Measure, the Dermatology Life Quality Index and evaluation of pruritus. More than half of patients with moderate-to-severe AD had depressive symptoms at baseline, 24% presented with moderate-to-severe depression and 3% had pronounced suicidal ideation. Systemic treatment of AD significantly reduced both depression and AD symptoms at 6 months, and this positive effect remained at 12 months. In conclusion, depressive symptoms are common among adults with moderate-to-severe AD. Systemic treatment of AD significantly reduced depressive symptoms in parallel with AD symptoms.

Key words: atopic dermatitis; atopic eczema; depression; suicidal ideation; drug therapy; epidemiology.

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Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases. A recent systematic review reported the 1-year prevalence of doctor-diagnosed AD assessed in adults in Europe in the year 2000 or later as ranging between 1.2% and 8.7% (1). The symptoms are characterized by dry skin, intensive itch, and recurrent eczematous lesions (2). A defective skin barrier, microbiome changes, dysfunctional T-cell-dominated skin inflammation and neuroinflammation involving itch, as well as environmental and genetic factors, are important in the pathogenesis (3). AD can have detrimental impacts on health-related quality of life (HRQoL) including severe sleep disturbance,

SIGNIFICANCE

Eczema or “atopic dermatitis” is one of the most common chronic skin disorders globally. The aim of the current study was to describe the occurrence of depression among adults with moderate-to-severe atopic dermatitis treated in a routine dermatological setting, and to compare depressive symptoms before and during systemic treatment. Data from a web-based Swedish national quality register comprising patients with atopic dermatitis on systemic treatment were analysed. More than half of patients with moderate-to-severe atopic dermatitis had depressive symptoms before treatment. Treatment of atopic dermatitis reduced both depressive symptoms, suicidal thoughts and symptoms of atopic dermatitis at 6 months, and this effect remained at 12 months.

psychosocial stress, limitations of daily activities and a negative occupational impact (4). Previous systematic reviews and meta-analyses have found an association between AD or AD severity and depression and suicidal ideation, although the results are conflicting (5–7). The underlying causes of these associations are not fully understood. It has been suggested that depression is a manifestation of physical and psychosocial burden from chronic disease (8).

Systemic treatment is indicated for severe cases of AD when first-line topical treatment and UV therapy have failed or are not feasible. Conventional systemic treatment includes methotrexate (MTX), azathioprine, ciclosporin and mycophenolic acid (9). Data on the effects of some of these drugs are limited and only ciclosporin is approved for AD in Europe. Dupilumab, a monoclonal antibody that inhibits interleukin-4 and interleukin-13 signalling, was approved in 2017 as the first biologic for AD (9). Real-world data have shown dupilumab to be effective and well-tolerated, although ocular adverse events are common (10). Patients with AD receiving dupilumab have shown significantly improved Hospital Anxiety and Depression Scale (HADS) scores in clinical trials (11), but no suicidal ideation data were reported. However, the effectiveness of treatment in clinical trials cannot always be generalized to treatment delivered in routine care. A motivating treatment team monitoring the therapy may affect outcomes. Furthermore, data on the prevalence and magnitude of depressive symptoms among patients with moderate-to-severe AD in a clinical setting are limited.

The primary aim of this study was to describe the prevalence and magnitude of depressive symptoms, including suicidal ideation, in adults before and during systemic treatment of moderate-to-severe AD in routine dermatological care. Moreover, we wanted to investigate the correlation between depression and clinician-reported AD severity, patient-reported AD severity, HRQoL and pruritus.

PATIENTS AND METHODS

Study design

This prospective real-world clinical cohort study used data from SwedAD, a web-based Swedish national quality register comprising patients with AD on systemic pharmacotherapy (12). The register includes demographic data, information on atopic comorbidity, previous and current treatments, and various eczema outcomes. Patient-reported data are collected via tablets or mobile phones at each patient visit and investigator-reported data are entered using a computer. The platform includes data from the Karolinska University Hospital from 10 January 2017 and was launched for national use on 1 September 2019. The current study analysed data from 1 June 2017 through 17 August 2021, based on 446 patients from 29 participating clinics.

Baseline findings were analysed at start of the first treatment registered in SwedAD (within 4 weeks before start and up to 2 weeks after start). Follow-up data at 6 months (range 3–9 months) and 12 months (≥ 10 months) were also analysed.

The study was approved by the Regional Ethics Review Board in Stockholm (2021/00394).

Outcome measures

The primary outcome measure was the Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S), a version of MADRS used for self-assessment of depression (13, 14). The questions in MADRS-S cover 9 items: depressed mood, feelings of unease, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimism and suicidal thoughts. Each item can score between 0 and 6, and thus the sum can range between 0 and 54 (15). The cut-off scores recommended by Svanborg & Ekselius, including the score for severe depression recommended by Snaith et al., were used in this study (no depression defined as 0–12, mild depression as 13–19, moderate as 20–34 and severe as ≥ 35) (16–18). For the suicidal thoughts item (number 9), 0 means "enjoys life or takes it as it comes" and 6 "explicit plans for suicide when there is an opportunity". Exhibiting marked suicidal ideation was defined as an item number 9 score ≥ 4 (suicidal thoughts common/better off dead) (19). Secondary outcomes were the Eczema Area Severity Index (EASI) (20), the Patient-Oriented Eczema Measure (POEM) (20), the Dermatology Life Quality Index (DLQI) (21) and pruritus intensity. A 0–10 cm visual analogue scale was initially used for self-assessment of the latter (22), but from September 2019 it was replaced by a 0–10 peak pruritus numerical rating scale (NRS-11) as recommended by HOME (Harmonising Outcome Measures for Eczema) (23, 24).

Covariates

Data on location of eczema during the last 12 months, emotional stress (if the patient felt that ongoing emotional factors influenced their current eczema), work limitations due to eczema and level of education were extracted from SwedAD. Emotional stress and data of work limitations were assessed within ≤ 28 days from start of treatment. Information about prescription of antidepressants was available from computerized medical records.

Study population

The inclusion criteria were as follows: (i) age ≥ 15 years, (ii) complete register data for MADRS-S at baseline, and (iii) initiation of systemic treatment during the study period. In total, 120 patients with complete baseline data were included. Patients who discontinued treatment due to adverse events (MTX $n=1$, dupilumab $n=3$), for unknown reason (MTX $n=1$), inadequate treatment response (MTX=1), or recently had been included in SwedAD with too short follow-up periods ($n=15$) or had started systemic treatment; however, with no follow-up data for unknown reason ($n=40$) at the 3-months or later were excluded from all follow-up analyses. Patients who discontinued treatment due to adverse events (MTX $n=1$), for unknown reasons (MTX $n=1$, dupilumab $n=2$), inadequate treatment response (MTX=1) or had any missing data ($n=18$) at 10 months or later were excluded from analyses at 12 months. The type of side-effects were not available in the dataset. At the 6-month follow-up, a total of 59 patients were included for further analysis. In total, 36 patients had complete records at baseline, 6 months and 12 months. Details for time periods are given in tables.

Statistical analysis

Baseline characteristics were expressed in proportions (%) of the total numbers of individuals observed and continuous data as medians with ranges. The Mann–Whitney U test was used for analyses of independent samples. Categorical data and dichotomous variables were compared, in terms of differences between proportions, using the χ^2 test. Dependent follow-up data between start and 6 months were investigated with the Wilcoxon signed-rank test. Friedman's repeated measurements analysis of variance (ANOVA) was used to analyse long-term follow-up, and pairwise comparison with Bonferroni correction to compare MADRS-S differences at start and follow-ups at 6 and 12 months. Adjusted means were calculated with repeated measurement ANOVA. The correlations between outcome measures were determined with Spearman's rank order correlation. Statistical significance was defined as p -values < 0.05 . All analyses were performed using SPSS, version 20 (IBM, Armonk, NY, USA).

RESULTS

Baseline patient characteristics

Among the 120 patients eligible for analyses, females represented 42.5% (**Table I**). Median age at entry was 39.0 years (range 17–82). Eight patients had already been on antidepressants for more than 3 months at baseline, and 2 started on antidepressants within 3 months before treatment start. At baseline, antidepressant use was significantly higher among females (21.9%) than males (6.0%). None of the patients on antidepressants were excluded from the analyses. Median MADRS-S (range) was 14.0 (0–50), with no significant difference between the sexes. In total, 35 (29.2%) met the criteria for a mild depression and 29 (24.2%) met the criteria for a moderate-to-severe depression. Among patients with complete data of MADRS-S items ($n=117$), 4 (3.4%) patients presented with marked suicidal ideation. The median EASI scores were significantly higher among males than females, but DLQI was significantly higher among females. There were no other significant differences of baseline characteristics with respect to sex. Among patients with data on

Table I. Baseline characteristics of patients with atopic dermatitis on systemic treatment

| | All cases n = 120 | Women n = 51 (42.5%) | Men n = 69 (57.5%) | p-value |
|---|----------------------|-------------------------|-----------------------|---------|
| Age, median (range) | 39.0 (17–82) | 38.0 (18–82) | 42.0 (17–77) | 0.561 |
| MADRS-S, median (range) | 14.0 (0–50) | 15.0 (0–44) | 12.0 (0–50) | 0.263 |
| Montgomery-Åsberg Depression Rating Scale-Self-report 0–12 p, No depression, n (%) | 56 (46.7) | 21 (41.2) | 35 (50.7) | 0.420 |
| Montgomery-Åsberg Depression Rating Scale-Self-report 13–19 p, Mild depression, n (%) | 35 (29.2) | 19 (37.3) | 16 (23.2) | |
| Montgomery-Åsberg Depression Rating Scale-Self-report 20–34 p, Moderate depression, n (%) | 24 (20.0) | 9 (17.6) | 15 (21.7) | |
| Montgomery-Åsberg Depression Rating Scale-Self-report ≥35 p, Severe depression, n (%) | 5 (4.2) | 2 (3.9) | 3 (4.3) | |
| Eczema Area Severity Index ^a , median (range) | 16.7 (1–50) | 12.7 (1–40) | 20.65 (1–50) | 0.009* |
| Patient-Oriented Eczema Measure ^b , median (range) | 22.0 (1–28) | 23.0 (5–28) | 21.0 (1–28) | 0.653 |
| Dermatology Life Quality Index ^c , median (range) | 15.0 (1–30) | 16.0 (2–28) | 12.0 (1–30) | 0.047* |
| Pruritus ^d (VAS/NRS-11), median (range) | 7.0 (0.1–10.0) | 7.8 (0.1–10.0) | 7.0 (0.4–10.0) | 0.143 |
| Education ^e , n (%) | | | | |
| ≤9 years | 9 (10.0) | 3 (8.1) | 6 (11.3) | 0.598 |
| >9–12 years | 43 (47.8) | 20 (54.1) | 23 (43.4) | |
| >12 years | 38 (42.2) | 14 (37.8) | 24 (45.3) | |
| Treatment, n (%) | | | | |
| Ciclosporin | 3 (2.5) | 2 (3.9) | 1 (1.4) | 0.441 |
| Dupilumab | 91 (75.8) | 36 (70.6) | 55 (79.7) | |
| Methotrexate | 26 (21.7) | 13 (25.5) | 13 (18.8) | |
| Ongoing emotional stress ^f , n (%) | 44 (48.9) | 20 (55.6) | 24 (44.4) | 0.302 |
| Facial eczema in the last 12 months ^g , n (%) | 73 (76.8) | 28 (75.7) | 45 (77.6) | 0.830 |
| Hand eczema in the last 12 months ^h , n (%) | 74 (77.9) | 30 (81.1) | 44 (75.9) | 0.550 |
| Work limitation due to eczema ⁱ , n (%) | 17 (28.3) | 6 (22.2) | 11 (33.3) | 0.342 |
| Alcohol consumption ^j , n (%) | | | | |
| Never | 23 (28.7) | 11 (35.5) | 12 (24.5) | 0.853 |
| 1 time/month or less | 12 (15.0) | 4 (12.9) | 8 (16.3) | |
| 2–4 times/months | 29 (36.3) | 11 (35.5) | 18 (36.7) | |
| 2–3 times/week | 10 (12.5) | 3 (9.7) | 7 (14.3) | |
| 4 times/week or more | 6 (7.5) | 2 (6.5) | 4 (8.2) | |
| Antidepressants ^k , n (%) | 10 (12.2) | 7 (21.9) | 3 (6.0) | 0.032* |

^aMissing n = 9. ^bMissing n = 2. ^cMissing n = 4. ^dPruritus: 0–10 cm visual analogue scale (VAS)/0–10 numerical rating scale (NRS-11. Missing n = 4. ^eMissing n = 30. ^fThe patients felt that ongoing emotional factors, e.g. conflicts, separation or work situation influenced their current atopic dermatitis. Data ≥ 28 days from treatment start excluded. Missing n = 30. ^gMissing n = 25. ^hMissing n = 25. ⁱStudents, pensioners and those unemployed excluded. Data ≥ 28 days from treatment start excluded. Missing n = 60. ^jMissing n = 40. ^kMissing n = 38.

Independent samples were tested with the Mann-Whitney U test. Pearson's χ^2 was used to compare the proportions between sexes for the following variables: education, treatment, ongoing stress, eczema location, work limitation, alcohol consumption and antidepressants. *Significant differences.

EASI score (n = 111), there was no significant difference in median EASI score between patients with moderate-to-severe depression (n = 27) (median EASI 19.0, range 1–47) and the patients with lower MADRS-S scores (n = 84) (median EASI 16.0, range 1–50).

Association at baseline between MADRS-S score and certain other variables

Work limitation related to AD was associated with significantly higher MADRS-S score (Table II). This also applied to patients perceiving that ongoing emotional factors, e.g. conflicts, separation or work situation, influenced their current AD. Patients who reported facial

eczema did not score significantly higher on MADRS-S compared with others; neither did patients with hand eczema. Alcohol consumption twice weekly or more was not associated with higher MADRS-S score.

Outcome measures at 6 months

All outcome measures among the 59 patients who completed follow-up at 6 months were significantly improved ($p < 0.001$) (Table III). The median MADRS-S change was –6.0 (range –32 to 11). The mean MADRS-S improvement remained significant when adjusting for sex, age and education ($p = 0.047$). Patients who were lost to follow-up (n = 61) at 6 months were comparable to patients in

Table II. Certain variables from patients with atopic dermatitis and the corresponding Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S) scores at baseline

| Variables, n = patients with complete data | MADRS-S | | | | p-value |
|--|--------------|----------------|-------------|----------------|---------|
| | Yes n (%) | Median (range) | No n (%) | Median (range) | |
| Work limitation due to eczema ^a , n = 60 | 17 (28.3) | 20.0 (0–50) | 43 (71.7) | 10.0 (0–31) | 0.002* |
| Ongoing emotional stress ^b , n = 90 | 44 (48.9) | 16.5 (7–44) | 46 (51.1) | 7.5 (0–50) | <0.001* |
| History of facial eczema in the last 12 months, n = 95 | 73 (76.8) | 14.0 (1–50) | 22 (23.2) | 12.0 (0–30) | 0.621 |
| History of hand eczema in the last 12 months, n = 95 | 74 (77.9) | 14.0 (0–50) | 21 (22.1) | 10.0 (0–25) | 0.560 |
| Alcohol consumption: 2–4 times a week or more, n = 80 | 16 (20.0) | 12.0 (0–23) | 64 (80.0) | 13.5 (1–50) | 0.445 |

^aStudents, pensioners and those unemployed excluded. Data ≥ 28 days from treatment start excluded. ^bThe patients perceived that ongoing emotional factors, e.g. conflicts, separation or work situation influenced their current atopic dermatitis. Data ≥ 28 days from treatment start excluded. p-values calculated with Mann-Whitney U test. *Significant differences.

Table III. Outcome measures among 59 patients with atopic dermatitis, treated with ciclosporin (n = 1), methotrexate (n = 10) or dupilumab (n = 48), who completed follow-up at 6 months

| | At start | 6 ^a months follow-up | p-values |
|--|----------------|---------------------------------|--------------------|
| MADRS-S, median (range) | 14.0 (0–50) | 5.0 (0–25) | < 0.001 |
| MADRS-S ^b , mean ± SD | 13.5 ± 9.9 | 6.5 ± 6.1 | 0.047 ⁹ |
| EASI ^c , median (range) | 20.5 (4–50) | 2.0 (0–23) | < 0.001 |
| POEM ^d , median (range) | 22.0 (4–28) | 6.0 (0–28) | < 0.001 |
| DLQI ^e , median (range) | 15.0 (1–30) | 3.0 (0–22) | < 0.001 |
| Pruritus ^f (VAS/NRS-11), median (range) | 7.1 (0.1–10.0) | 1.8 (0.0–8.0) | < 0.001 |

^aValues collected at 6 months ± 3 months. ^bMissing n=8 (cases missing data on education). ^cMissing=9. ^dMissing=2. ^eMissing=2. ^fMissing=1. ^gAdjusted for age, sex and education. Adjusted mean calculated with repeated measurement analysis of variance (ANOVA).

MADRS-S: Montgomery-Åsberg Depression Rating Scale-Self-report; EASI: Eczema Area Severity Index; POEM: Patient-Oriented Eczema Measure; DLQI: Dermatology Life Quality Index; Pruritus: 0–10 cm visual analogue scale (VAS)/0–10 numerical rating scale (NRS-11). p-values calculated with Wilcoxon's signed-rank test.

the cohort included for longitudinal analyses (MADRS-S at baseline was not significantly different). Moreover, the EASI score at start was not significantly different between those lost to follow-up (n = 55) and patients included for further analysis of the EASI score (n = 50). In a sensitivity analysis, the significant MADRS-S reduction between start and 6 months remained when all patients who were on antidepressants (n = 8) during the study period (data not shown) were excluded. Six patients who had used antidepressants for at least 3 months before treatment start and throughout follow-up significantly improved their MADRS-S score from median 15.5 (range 8–21) to median 9.0 (range 2–16), $p=0.027$. During the observation period, 41 (82.0%) patients achieved at least a 50% improvement in EASI score from baseline (EASI-50), 35 (70.0%) achieved at least a 75% improvement (EASI-75) and 20 (40.0%) achieved at least a 90% improvement (EASI-90). Patients who achieved EASI-90 did not have a significantly different median MADRS-S score (median MADRS-S 2.5, range 0–23) compared with patients who did not achieve EASI-90 (median MADRS-S 6.0, range 0–25). A similar finding was seen in responders and non-responders for EASI-75 and EASI-50, respectively. Three out of 4 patients with severe suicidal ideation at baseline had complete 6-month follow-up data. They improved their item 9 scores in MADRS-S to ≤ 2 ("enjoys life or takes it as it comes"/"only fleeting suicidal thoughts").

The median MADRS-S score at start was 15.0 (range 2–26), 13.0 (range 0–50) and 13.0 in the treatment group with MTX (n = 10), dupilumab (n = 48) and ciclosporin (n = 1), respectively (Fig. 1). The median MADRS-S score at start did not differ significantly between patients treated with MTX or dupilumab, but was significantly lower in the dupilumab group compared with the MTX group at the 6-month follow-up ($p=0.005$). There was a statistically significant reduction in MADRS-S score in the dupilumab group (–6.5, range –32 to +4, $p<0.001$) but not in the MTX group (median reduction –4.0, range –9 to 11, $p=0.221$).

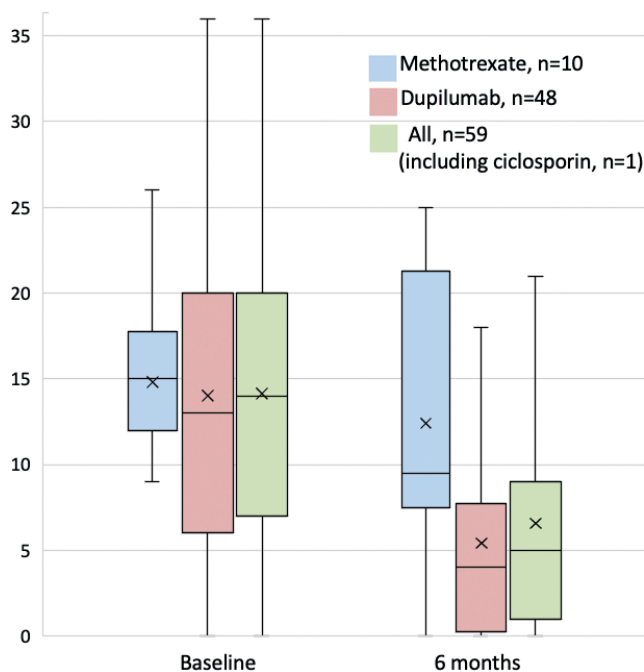


Fig. 1. Boxplot showing medians, interquartile ranges and ranges of Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S, y-axis) at baseline and follow-up at 6 months among 59 adults with atopic dermatitis on systemic treatment. Means marked with x.

Outcome measures at 12 months

Among the 36 participants who completed the 12-month follow-up (Table IV), there was a significant effect of systemic treatment (all drugs) on MADRS-S compared with baseline (test statistic=23,953, Df =2, $p<0.001$). Follow-up comparisons indicated that the MADRS-S pairwise difference was significant between start and 6 months ($p<0.001$) and between start and 12 months ($p<0.001$), but not between 6 and 12 months.

MADRS-S items (0–6 months)

Sleep impairment scored highest at start with median 3.0 (range 0–6). All medians of the items (aspects of depressive symptoms) in MADRS-S improved significantly between start and 6 months, as seen in Fig. 2 ($p<0.05$).

Table IV. Effect of systemic treatment (dupilumab n = 32, methotrexate n = 4) on outcome measures among 36 patients with atopic dermatitis who completed follow-up at 6 and 12 months

| | At start Median (range) | At 6-month follow-up ^a Median (range) | At 12-month follow-up ^b Median (range) | Crude p-values |
|-------------------|----------------------------|--|---|-------------------|
| MADRS-S | 12.5 (2.0–50.0) | 6.0 (0.0–23.0) | 5.5 (0.0–31.0) | < 0.001 |
| EASI ^c | 26.0 (4.0–50.0) | 2.0 (0.0–23.0) | 2.0 (0.0–18.0) | < 0.001 |
| POEM ^d | 22.0 (5.0–28.0) | 6.0 (0.0–18.0) | 3.0 (0.0–22.0) | < 0.001 |
| DLQI | 15.0 (2.0–30.0) | 2.0 (0.0–22.0) | 2.0 (0.0–24.0) | < 0.001 |
| Pruritus | 7.1 (0.1–10.0) | 1.6 (0.0–8.0) | 1.2 (0.0–8.0) | < 0.001 |

^aValues collected at 6 ± 3 months. ^bThe 12-month follow-up range for EASI was 9–23 months, and for the other outcomes 9–17 months. ^cMissing=5. ^dMissing=1. MADRS-S: Montgomery-Åsberg Depression Rating Scale-Self-report; EASI: Eczema Area Severity Index; POEM: Patient-Oriented Eczema Measure; DLQI: Dermatology Life Quality Index; Pruritus: 0–10 cm visual analogue scale (VAS)/0–10 numerical rating scale (NRS-11). p-values calculated with Friedman's repeated measurements analysis of variance.

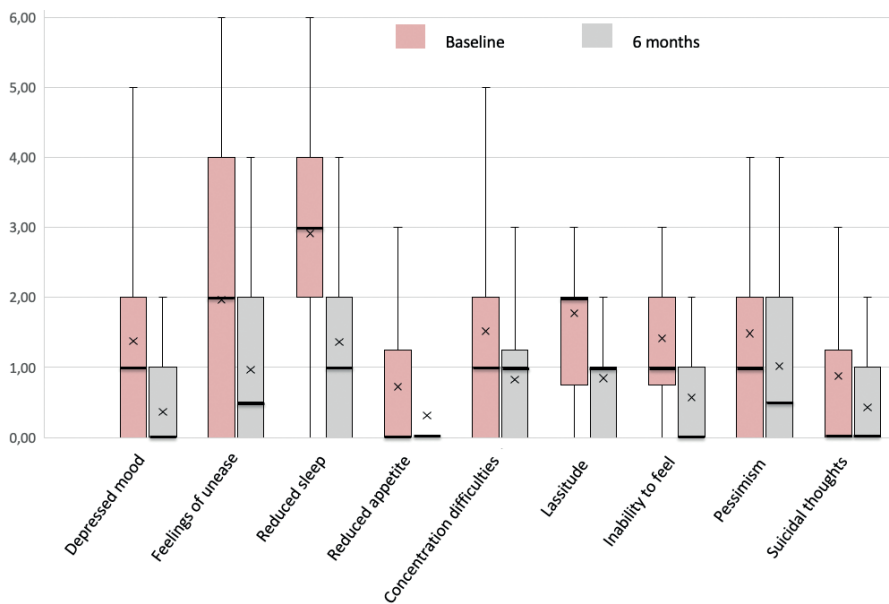


Fig. 2. Boxplot showing medians, interquartile ranges and ranges of items in Montgomery-Åsberg Depression Rating Scale-Self-report (MADRS-S) at baseline and follow-up at 6 months among 58 adults^a with atopic dermatitis on systemic treatment. Means marked with x. ^aOne patient excluded since only total score of MADRS-S was recorded, not scores on each item.

However, the median scores of concentration difficulties, reduced appetite and suicide ideation were equal at baseline and 6 months. The significant reductions in these items were related to the different score distributions at start and follow-up. When excluding the item of sleeplessness, the median MADRS-S score at start was 10.0 (range 0–44) and the median MADRS-S change between 0 and 6 months was (–4.0, range –30 to 10, $p < 0.001$). One patient was excluded since only the total MADRS-S score was recorded, i.e. not the score of each item.

Correlation between MADRS-S and other outcomes (0–6 months)

Among patients with complete data of outcome measures 0–6 months ($n = 50$), Spearman's correlation coefficients for registered MADRS-S scores (at start and 6 months) revealed significant correlation with EASI ($r = 0.380$, $p < 0.001$), POEM ($r = 0.611$, $p < 0.001$), DLQI ($r = 0.692$, $p < 0.001$) and pruritus intensity ($r = 0.520$, $p < 0.001$). Among patients with scores on each MADRS-S item and other outcomes ($n = 49$), the correlations remained significant when the item sleeplessness was excluded (EASI ($r = 0.348$, $p < 0.001$), POEM ($r = 0.561$, $p < 0.001$), DLQI ($r = 0.656$, $p < 0.001$) and pruritus intensity ($r = 0.463$, $p < 0.001$)). Furthermore, there was significant correlation between the responses to questions about sleep disturbance in POEM and in MADRS-S ($n = 48$) ($r = 0.399$, $p < 0.001$).

DISCUSSION

More than half of patients with moderate-to-severe AD eligible for systemic treatment had depressive symptoms, 24% presented with a moderate-to-severe depression and 3% with pronounced suicidal ideation. The main

finding was that systemic treatment of AD significantly reduced depressive symptoms at 6 months; this positive effect remained stable at 12 months. The MADRS-S score to evaluate depressive symptoms among patients with AD may be confounded by the item sleeplessness if itch causes sleep disturbance. However, all aspects (items) of depressive symptoms in MADRS-S, including suicidal ideation, improved significantly during systemic AD treatment. Sleep disturbance was the aspect with the highest MADRS-S value at baseline. There were significant correlations between MADRS-S and POEM, DLQI and EASI, respectively, during the study period. This also holds true when the item sleeplessness was excluded from the total score. We found a significant association of higher MADRS-S scores with work limitations due to AD, and if patients perceived that emotional stress influenced their AD, but not with hand or facial AD.

Studies exploring the impact of systemic AD treatment on depression and/or depressive symptoms are limited outside clinical trials. A Japanese study has shown that "tight control" of AD with oral ciclosporin and topical glucocorticoids reduced depressive symptoms (7). The current results are in line with those of a phase III clinical trial and a previous real-life study of dupilumab that demonstrated significant reduction in depressive symptoms (11, 25). It was not possible to compare the estimates across studies due to differences in study design. Moreover, HADS, which is commonly used in clinical trials, does not specifically address suicidal ideation. In Sweden, dupilumab remains a second-line systemic therapy to be given in case of contraindications for or failure of other systemic treatments. Almost all patients in this study had tried another systemic treatment within 2–6 weeks before starting dupilumab. Therefore, MADRS-S scores at start among dupilumab patients may have included a carry-over effect from previous systemic treatment.

Altogether, the study suggests that dupilumab was more effective than MTX in reducing depressive symptoms, as the median MADRS-S score was significantly lower in the dupilumab group at the 6-month follow-up.

There are several possible explanations as to why systemic treatment could reduce depressive symptoms. Itch and sleep disturbances appear to worsen with AD severity (26, 27). Several studies have identified insomnia as an independent risk factor for the development of depression, and sleep disturbance is a core symptom of major depressive disorder (28). Other factors assumed to cause depression among patients with AD include social isolation, stigmatization due to cosmetic appearance, restrictions in occupation and sport activities, problems in relationship and sexuality, and financial costs (29). Moreover, varying proinflammatory cytokine levels have been observed in patients with chronic AD, and proinflammatory cytokines have been related to changes in the metabolism of neurotransmitters, including serotonin, norepinephrine and dopamine (30). Some authors have suggested that variation in the cytokine profile in subjects with AD may increase the risk of depression (31). Thus, effective systemic treatment of AD, targeting both the skin inflammation, itch and sleeping disturbances, and perhaps neuroinflammatory pathways yet to be discovered, might reduce depressive symptoms.

A Swedish population-based study from 2013 suggested that, at any given time-point, 10.8% of the Swedish population was experiencing a clinically significant depression (32). A recent meta-analysis among adults and children with AD found that any depression was more common in persons with than without AD (20.1% vs 14.8%), with higher odds of depression in adults (7). In the current study, the prevalence of depressive symptoms was higher than in the meta-analysis. This may be explained by the current study population consisting of adults with moderate-to-severe AD. Observations from clinical trials have suggested a severity-dependent relationship between AD and depression (6). A Danish cross-sectional study found a positive association between moderate-to-severe AD (defined as patients on systemic treatment) and the use of antidepressants (33). In contrast, a US cross-sectional study did not find a severity-dependent relationship between AD and depression (34). The current study found a lower prevalence of suicidal ideation compared with a recent meta-analysis (3% vs. 12.2%) (7). Differences may be due to diversity in study design, age distribution for the study population, definitions of marked suicidal ideation and other outcome measures. The current results were similar to those of a German cross-sectional study in which 7/181 (3.9%) exhibited symptoms indicating a suicidal crisis (35). In the current study, 3 patients with marked suicidal ideation radically improved their scores of suicidal ideation during systemic AD treatment. In addition, patients treated with antidepressants > 3 months at baseline im-

proved in depressive symptoms at the same magnitude as patients without antidepressant treatment. This suggests that depressive symptoms in patients with moderate-to-severe AD may benefit from systemic AD treatment in addition to traditional antidepressants.

Worldwide, and across the lifespan, depression is almost twice as common in females as in males (36). In Sweden, the prevalence of a clinically significant depression was estimated at 12.9% among females and 8.3% among males in 2013 (32). AD in females has been linked to more depressive symptoms than AD in males (37). Interestingly, the current study did not find any baseline differences between sexes as regards MADRS-S. Males had a clinically more severe AD and thus might have had more depressive symptoms in the current study.

The strengths of the current study included the use of well-validated outcome measures. The study was performed in a routine secondary/tertiary dermatological care setting, meaning that the results are representative for how systemic treatment affects clinical signs of depression in such daily praxis. However, the study also had limitations. The patients completed assessments with MADRS-S, but, unfortunately, we did not have a complementary measure of depressive symptoms assessing the DSM-IV criteria of depression. On the other hand, a Swedish study has compared MADRS-S with Beck Depression Inventory II, one of the most commonly used instruments for screening and diagnosis of depression. It found good comparability and reliability across severity of depression and suggested that MADRS-S can be used for both diagnostic assessment and follow-up (38). Another limitation was that many eligible patients were excluded due to missing data (e.g. patients who stopped treatment, changed treatment or had incomplete register data).

In conclusion, the current study found a high prevalence of depression among patients with moderate-to-severe AD in secondary/tertiary dermatological routine care. Systemic treatment of AD significantly reduced depressive symptoms at 6 and 12 months in parallel with relieving AD manifestations. Greater awareness of the co-morbidity with depression among patients with AD and, based on the current results, proper management of the skin disease might have impact on the depressive symptoms.

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Conflicts of interest. LUI has received speaker honoraria from ACO, Sanofi-Genzyme and Abbvie, and has participated as an expert in meetings with Lilly. AS is an employee of iCON plc, a contract research organization. AS has received speaker honoraria from Janssen-Cilag. ML has received speaker honoraria from

Sanofi-Genzyme. CFW has participated as unpaid expert in meetings with Sanofi-Genzyme and AbbVie. MB has received research funding from Sanofi-Genzyme, speaker honoraria from Novartis, AstraZeneca, AbbVie, Leo Pharma, and Celgene, and been part of the advisory board for Sanofi-Genzyme, Novartis, Lilly, AbbVie, and Leo Pharma. EKJ has received speaker honoraria and/or been a consultant for Sanofi-Genzyme, Leo Pharma, ACO, Novartis, AbbVie, and Galenica.

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