

ORIGINAL ARTICLE

Recent trends in disease severity and quality of life instruments for patients with atopic dermatitis: A systematic review

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Background: A significant number of instruments exist that are aimed at quantifying atopic dermatitis (AD) outcomes.

Objective: We sought to assess recent trends in the use of disease severity and quality of life (QOL) outcome instruments in randomized controlled trials (RCTs) conducted on patients with AD between July 2010 and July 2015.

Methods: A total of 540 nonduplicate records were identified through searches of Scopus and Ovid MEDLINE. Included studies were RCTs conducted on humans with AD that were published in English between July 2010 and July 2015 and that reported the results of disease severity or QOL outcome measures.

Results: All of the 135 included studies assessed disease severity. Only 45 studies assessed QOL. Sixty-two disease severity measures and 28 QOL scales were identified.

Limitations: This study was limited by its timeframe of 5 years and by the exclusion of non-RCTs and gray literature.

Conclusion: Disease severity and QOL outcome measures are instrumental in evaluating AD treatment efficacy. The number of such tools used in RCTs on patients with AD continues to rise. Standardization of outcomes instruments is essential for comparability among studies and improved quality of evidence. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2016.07.002>.)

INTRODUCTION

Atopic dermatitis (AD; also known as atopic eczema or eczema) is a chronic inflammatory, pruritic skin disease with significant quality of life (QOL) consequences for both patients and families.¹⁻³ Affecting $\leq 30\%$ of children and 10% of adults,⁴ AD presents a major global public health concern of increasing magnitude.^{5,6} Recent advances in

understanding the molecular phenotype of AD have opened the door to potential new treatment avenues,⁷ making the use of reliable outcomes measures in AD therapeutic trials more important than ever.

A plethora of instruments aimed at quantifying AD outcomes exist. Given the often concurrent physiologic and psychological burdens of AD,¹⁻³ both disease severity and QOL measures are fundamental to

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Funding sources: None.

Conflicts of interest: None declared.

Accepted for publication July 5, 2016.

Reprints not available from the authors.

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 Published online September 8, 2016.

0190-9622

Published by Elsevier on behalf of the American Academy of Dermatology, Inc.

<http://dx.doi.org/10.1016/j.jaad.2016.07.002>

patient evaluation and care. A systematic review by Rehal and Armstrong⁸ identified a total of 20 disease severity scales and 14 QOL indices used in 382 randomized controlled trials (RCTs) of AD treatment between 1985 and July 2010. The most frequently used disease severity scale was the Scoring Atopic Dermatitis (SCORAD) index,⁹ followed in frequency of use by the Eczema Area and Severity Index (EASI),¹⁰ both of which increased in use between 2005 and 2010. While only 67 RCTs reported QOL outcomes, the use of such instruments expanded over the time period studied, possibly indicating an increased recognition of the need to account for QOL when evaluating patient welfare. To our knowledge, there has been no systematic review describing trends in outcomes measures of AD trials published since July 2010.

The purpose of this study was to assess by systematic review recent trends in disease severity and QOL outcome instruments used in RCTs on patients with AD that were conducted between July 2010 and July 2015. Specifically, we sought to establish the following: 1) the proportion of reviewed studies using disease severity or QOL outcome measures; 2) the total number and frequency of use of disease severity scales; and 3) the total number and frequency of QOL instruments used.

Search strategy and criteria

Comprehensive searches of the literature were conducted by two authors (MKH and AKP) using the Scopus, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE bibliographic databases for the period of January 1, 2010 through July 31, 2015. Searches used combinations of the key terms “atopic dermatitis,” “randomized controlled trial,” “quality of life,” and “severity of illness index” (Tables I and II). Two reviewers (MKH, AKP) independently assessed the eligibility of identified records. Included studies were human subject RCTs on AD published in English between July 1, 2010 and July 31, 2015 that reported the results of disease severity or QOL outcome measures. The search databases were filterable by time periods of years but not months (Tables I and II), and studies published between January 2010 and July 2010 were therefore manually excluded.

Study selection

Six hundred forty-six records were identified (175 from Scopus and 471 from Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE), of which 540 were non-duplicate records (Fig 1). Of the 405 studies excluded, 53 were published before July 2010, 195 were not RCTs, 58 did not investigate AD treatment, 39 were not human studies, 17 were not in English, and 43 did not report disease severity or QOL outcome measures. The remaining 135 RCTs¹²⁻¹⁴⁶ were included in the systematic review.

RESULTS

All of the 135 included RCTs assessed disease severity. Sixty-seven (50%) included studies used >1 disease severity scale. Only 45 (33%) studies reported QOL

outcomes. Fifteen (11%) studies used >1 QOL measure. The proportion of published RCTs that assessed QOL peaked in 2012 (Fig 2).

Sixty-two disease severity scales were used in the 135 reviewed RCTs (Table III). The most frequently used disease severity scale was the SCORAD index,⁹ which was used in 79 studies. The second most common disease severity instrument was the visual analogue scale (VAS) for pruritus (n = 30). These were closely followed by the Investigator's Global Assessment (IGA) tool (n = 29) and the EASI¹⁰ (n = 28). There were no discernable trends in use of the top four disease severity scales by publication year. Forty-five of the identified disease severity scales were used in only 1 study.

From the 45 studies that assessed QOL, a total of 28 QOL measures were identified (Table IV). The most common QOL instrument, the Dermatology Life Quality Index (DLQI),¹⁴⁷ was used in 20 RCTs. The second most frequent measure, the Infants' Dermatology Quality of Life Index (IDQOL),¹⁴⁸ was used in only 8 RCTs. These were followed by the Children's Dermatology Life Quality Index¹⁴⁹ (CDLQI; n = 6) and the Dermatitis Family Impact (DFI) questionnaire¹⁵⁰ (n = 5). Twenty-one of the identified QOL instruments were used in only 1 study.

DISCUSSION

Our systematic review identified a total of 62 disease severity scales from the 135 included studies. This is a drastic increase from the 20 disease severity

CAPSULE SUMMARY

- Many available measures exist for quantifying atopic dermatitis outcomes.
- This systematic review identified 62 disease severity and 28 quality of life instruments used in randomized controlled trials on atopic dermatitis between July 2010 and July 2015.
- The increasing heterogeneity of reported outcomes hinders their comparability and translation to clinical practice.

Abbreviations used:

AD:	atopic dermatitis
BSA:	body surface area
CDLQI:	Children's Dermatology Life Quality Index
DFI:	Dermatitis Family Impact
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
HOME:	Harmonising Outcome Measures for Eczema
IDQOL:	Infants' Dermatology Quality of Life Index
IGA:	Investigator's Global Assessment
RCT:	randomized controlled trial
SCORAD:	Scoring Atopic Dermatitis
VAS:	visual analogue scale

scales identified in Rehal and Armstrong's review⁸ of 382 RCTs on AD treatment published between 1985 and July 2010. Similar to Rehal and Armstrong's findings,⁸ the SCORAD index⁹ remained the most popular disease severity instrument, appearing in 59% of reviewed studies. This severity index analyzes 3 areas: the extent of disease, the intensity of disease, and the patient's subjective symptoms. Involved body surface area (BSA) is estimated using the rule of nines. Intensity scores from 0 to 3 (none to severe) are assigned for erythema, edema/papulation, oozing/crusting, excoriations, dryness (assessed on uninvolved areas), and lichenification. Lastly, the index assesses the subjective symptoms of pruritus and sleep loss, with both evaluated on a scale from 0 to 10. The total SCORAD score (maximum of 103) is calculated as: $BSA/5 + 7(\text{the sum of intensity scores})/2 + \text{the subjective symptom scores}$.

While the EASI¹⁰ dropped 2 spots to the fourth most widely used scale, the total proportion of RCTs using the index increased from 16% identified by Rehal and Armstrong⁸ to 21% in our review. The EASI¹⁰ assesses two areas: the extent of disease and objective signs. The extent of disease is based on a percentile estimate of the involved BSA converted to a score from 0 to 6 for 4 areas: head and neck, trunk, upper limbs, and lower limbs. Severity is scored from 0 to 3 for the objective signs of erythema, papulation/edema, excoriation, and lichenification. The total score is weighted based on these factors, with a maximum score of 72.

Among the 45 identified disease severity scales used in only 1 study, there was frequent overlap in naming and content of instruments. For instance, despite different names, both the Target Lesion Symptom Score⁵⁰ and the Eczema Severity Score⁹⁴ included physician rankings of severity from 0 to 3

for erythema, papulation, excoriation, and lichenification. In addition, the Patient Global Assessment¹¹⁹ and the differing versions of the Physician Global Assessment^{31,50,109} were each abbreviated and referred to as PGA. Such confusing similarities add to the challenges readers face when trying to compare study outcomes amidst rising numbers of disease severity instruments.

Further challenging severity assessment in AD research is the lack of standardization of specific tools. This is especially apparent in the use of global assessments. A systematic review by Futamura et al¹⁵¹ found large variability between studies in the content, scales, directions for use, and defined thresholds for success of global assessments. Our review identified 11 severity scales labeled as "global" (Table III), with the most common being the IGA. The origin and inception of the IGA is unknown,¹⁵² and it is unclear how many versions of the same-named tool exist. As emphasized by Futamura et al,¹⁵¹ variations in global assessments hinder meaningful comparisons between studies, making it difficult to interpret data and make informed clinical decisions. They therefore called for a standardized method of globally assessing severity in AD.

In addition to the excessive number of outcome instruments used, the lack of validation and reliability testing of many of these indices further challenges comparability between AD trials.^{8,152,153} In an effort to reduce the heterogeneity of published outcomes, the Harmonizing Outcome Measures for Eczema (HOME) group recommended in 2014 that all trials use at a minimum the EASI to quantify the severity of AD clinical signs.¹⁵⁴ We found no discernable increase in the use of the EASI after the HOME group's proposal. However, the design and planning of many of our included studies likely preceded the publication of their proposal, and so future longer-term reviews are necessary to fully assess the impact of these recommendations.

Similar challenges with disease severity instruments have been described in psoriasis research. A systematic review by Naldi et al¹⁵⁵ found 44 different scoring systems used in 171 randomized clinical trials on psoriasis. Despite identifying 44 scales, there was no documented evidence that any of them addressed outcomes important to the patient, and they called for improved reporting quality of RCTs. Puzenat et al¹⁵⁶ determined that only 6 of these 44 psoriasis clinical severity scores were validated and standardized. They emphasized the need for standardization of severity instruments for psoriasis and the inclusion of QOL measures. Feldman and Krueger¹⁵⁷ also emphasized the importance of QOL measures and the difficulty of objectively measuring psoriasis

Table I. Search strategy for Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE

Search number	Search strategy	No. of records
1	(Atopic dermatit* or atopic neurodermatit* or disseminated neurodermatit* or atopic eczem* or infantile eczem*).mp.	16,708
2	Exp dermatitis, atopic/	15,190
3	1 or 2	20,927
4	((Qualit* adj2 life) or IDQOL or Children* Dermatology Life Quality Index or CDLQI or Infant* Dermatology Quality of Life or IDQOL or Parent* Index of Quality of Life in Atopic Dermatit* or PIQOL-AD or Quality of Life Index for Atopic Dermatitis or QOLIAD or Short Form Health Survey or Health Survey or SF-36 or SF36 IR SF-12 or SF12 or Parent* of Children with Atopic Dermatit* or PQOL-AD or German Instrument for the Assessment of Quality of Life in Skin Diseases or DIELH or Eczema Disability Index or EDI or SKINDEX or (outcome* adj2 measure*) or Dermatological Health-Related Quality of Life or HRQoL or disabilit* or (disabilit* adj2 index) or ITCHYQOL).mp.	573,953
5	Exp "Quality of Life"/or exp "Outcome and Process Assessment (Health Care)"/or exp "Outcome Assessment (Health Care)"/or exp Treatment Outcome/or exp Disability Evaluation/or exp Questionnaires/	1,204,256
6	4 or 5	1,531,076
7	((severity adj2 scale*) or (severity adj2 score) or (severity adj2 scores) or (severity adj2 scoring) or (severity adj2 index) or (itch adj2 severity) or (itch adj2 index) or (pruritis adj2 scale) or (assessment adj2 global) or (eczema adj2 area) or (eczema adj2 severity) or (eczema adj2 score) or (sign adj2 score) or (visual adj2 scale) or (intensity adj2 score) or SCORAD or EASI or IGA or SASSAD or IGADA or LSS or VAS or TSS or PGA or IISA or ADSI or ISGA or NESS or IGAS or DASI or ADASI or TBSA).mp.	147,953
8	Exp "Severity of Illness Index"/	184,985
9	7 or 8	320,758
10	(Random* or RCT or randomized control* trial* or (clinical adj2 trial*) or controlled or (controlled adj2 trial)).mp.	1,805,965
11	Exp randomized controlled trial/	407,848
12	10 or 11	1,805,965
13	6 or 9	1,742,753
14	3 and 12 and 13	1346
15	Limit 14 to yr = "2010 - Current"	471

ADASI, Atopic Dermatitis Area and Severity Index; ADSI, Atopic Dermatitis Severity Index; CDLQI, Children's Dermatology Life Quality Index; DASI, Dyshidrotic Eczema Area and Severity Index; DIELH, German Instrument for the Assessment of Quality of Life in Skin Diseases; EASI, Eczema Area and Severity Index; EDI, Eczema Disability Index; HRQoL, Dermatological Health-Related Quality of Life; IDQOL, Infant's Dermatology Quality of Life; IGA, Investigator's Global Assessment; IGADA, Investigator's Global Atopic Dermatitis Assessment; IGAS, Investigator's Global Assessment Score; IISA, Intensity Item Score Aggregate; ISGA, Investigator's Static Global Assessment; LSS, Leicester sign score; NESS, Nottingham Eczema Severity Score; PGA, Physician's Global Assessment; PIQOL-AD, Parent's Index of Quality of Life in Atopic Dermatitis; PQOL-AD, Parents of Children with Atopic Dermatitis; QOLIAD, Quality of Life Index for Atopic Dermatitis; SCORAD, Severity Scoring of Atopic Dermatitis; SF-36, Short Form Health Survey; SASSAD, Six Area, Six Sign Atopic Dermatitis; TBSA, Total Body Severity Assessment; TSS, total severity score; VAS, visual analogue scale.

Table II. Search strategy for Scopus

Search number	Search strategy	No. of records
1	TITLE-ABS-KEY (randomized control trial*)	147,528
2	TITLE-ABS-KEY (RCT)	14,249
3	1 OR 2	157,976
4	TITLE-ABS-KEY (atopic dermatitis)	31,958
5	3 AND 4	407
6	5 AND (LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010))	175

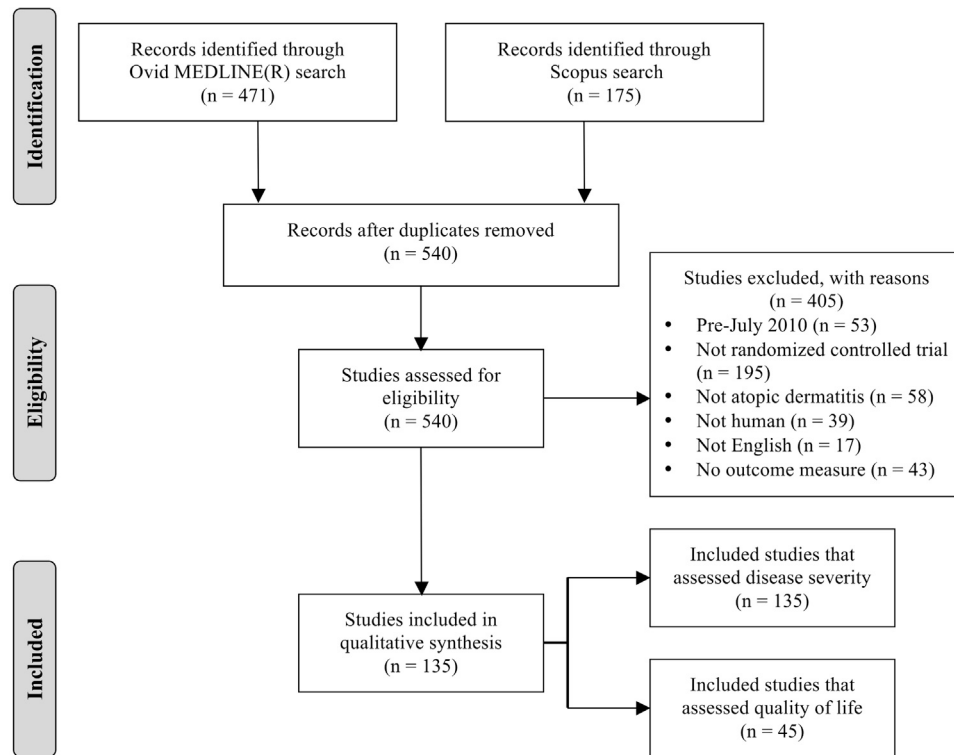


Fig 1. The search process is depicted using a flow diagram adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹¹

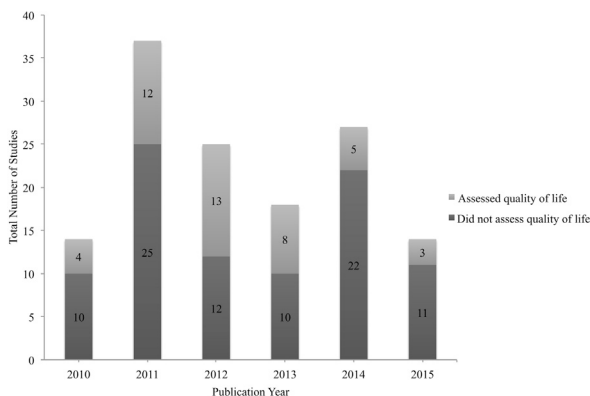


Fig 2. A column chart depicts the total number of included studies by publication year, with the number of studies that did and did not assess quality of life illustrated for each year.

outcomes. They noted that there is no single “best” available severity scale, and suggested use of the Psoriasis Area and Severity Index¹⁵⁸ in conjunction with physician global assessment and QOL tools in order to provide a comprehensive view of the impact of the disease on the patient.

An analogous quandary exists with outcomes instruments assessing acne. There are 2 major methods of assessing outcomes of acne therapy in clinical trials: grading and lesion counting.^{159,160} Grading compares the global severity of the patient to that of a

standardized text description or photograph; lesion counting involves counting the number of lesions within a portion of or on the entire face.¹⁵⁹ In a systematic review including 18 RCTs on acne therapy, Zarchi and Jemec¹⁶⁰ found 25 different methods of reporting lesion counts, 25 different methods of assessing changes in grading, and 9 different methods of reporting acne severity at baseline. Unlike with psoriasis, however, acne clinical trials rarely assess patient QOL. In their review, Zarchi and Jemec¹⁶⁰ found that QOL was only assessed in 3 trials, with each trial using a different scale. They recommended combined use of lesion counting, Physician’s Global Assessment, and QOL measures to provide a comprehensive understanding of acne treatment efficacy. They also called for international standardization of outcomes instruments.

Despite the documented burden of AD, the field continues to lack frequent reporting of QOL outcomes. Only 33% of the 135 RCTs in our review assessed QOL. This is up from the 18% of RCTs on AD that reported QOL outcomes between 1985 and July 2010,⁸ perhaps signifying gradually increased attention to patient emotional well-being. However, with this increase has also come a doubling in the number of published QOL tools from 14 identified by Rehal and Armstrong⁸ to 28 identified in our review. The 4 most widely used measures remained—albeit in a new order—the

Table III. Identified disease severity scales

Disease severity scale	No. of studies used in
Severity Scoring of Atopic Dermatitis (SCORAD)	79
Visual analogue scale (VAS) pruritus	30
Investigator's Global Assessment (IGA)	29
Eczema Area and Severity Index (EASI)	28
Affected body surface area	9
Objective SCORAD	8
VAS sleep disturbance	8
Patient-Oriented Eczema Measurement (POEM)	5
Hand Eczema Severity Index (HECSI)	3
VAS severity	3
5-point Physician's Global Assessment (PGA)*	2
Six Area, Six Sign Atopic Dermatitis (SASSAD)	2
Three Item Severity score (TIS)	2
Atopic Dermatitis Severity Index (ADSI)	2
4-point scale for itching	2
Pruritus Numerical-Rating Scale (PNRS)	2
Pruritus Categorical Response Scale (PCRS)	2
Target lesion assessment	1
4-point Severity Scoring System by the Japanese Dermatological Association (SSS-JDA)	1
Physician Assessment of Individual Signs (PAIS)	1
Atopic Dermatitis Area and Severity Index (ADASI)	1
Eczema Severity Score (ESS)	1
Investigator's Global Assessment of Improvement (IGAI)	1
Investigator's Pruritus Severity Assessment (IPSA)	1
Japanese Dermatological Association Scoring System (JDASS)	1
Patient's Self Global Assessment (PSGA)	1
Patrizi et al clinical signs scale	1
Subject Global Assessment of Improvement (SGAI)	1
Target Lesion Symptom Score (TLSS)	1
5-D pruritus scale	1
4-point scale for overall skin condition	1
4-point scale for sleep disturbance	1
VAS xerosis	1
Skin Detective Questionnaire	1
Breuer et al disease severity index	1
Koppelhus et al 6-point overall global assessment	1
Matsumoto et al 5-point itch improvement scores	1
Severity index from the Ministry of Health, Labor, and Welfare	1
Pruritus Interference Numeric Rating Scale (PINRS)	1
Subject's Global Impressions of Change in Pruritus (SGICP)	1
Weber et al 6-point investigator assessment of improvement	1
Korting et al severity score	1
Draeos et al target lesion severity rating	1
Wong et al patients' assessment of overall response	1
Rajka-Langeland score	1
Itch Behavioral Rating Scale	1
Trookman et al subjective irritation symptom scale	1
Panahi et al pruritus score	1
Partial Eczema Area and Severity Index (pEASI)	1
Patient-oriented SCORAD (po-SCORAD)	1
Severity Scale Score (SSS)	1
Emer et al subjective self-assessment scale	1
Eppendorf Itch Questionnaire (EIQ)	1
Herzog et al subject assessment of pruritus relief	1
Onumah and Kircik subjective symptom questionnaire	1

Continued

Table III. Cont'd

Disease severity scale	No. of studies used in
Patients Self-Assessment (PSA)	1
5-point Skin Severity Score from the Japanese Dermatological Association	1
Patient Global Assessment (PaGA)	1
6-point Patient Global Assessment (PGA)*	1
van Gils et al Patients' Global Assessment	1
Furie et al severity of targeted lesion	1
6-point Physicians Global Assessment (PGA)*	1

*Each instrument was abbreviated PGA.

Table IV. Identified quality of life scales

Quality of life scales	No. of studies used in
Dermatology Life Quality Index (DLQI)	20
Infant's Dermatology Quality of Life Index (IDQOL)	8
Children's Dermatology Life Quality Index (CDLQI)	6
Dermatitis Family Impact (DFI)	5
EuroQoL 5-Dimension (EQ-5D)	4
Skindex-29	2
Beck Depression Inventory (BDI)	2
Quality of Life Index for Atopic Dermatitis (QoLIAD)	1
Health Utilities Index Mark 3 (HUI3)	1
Interaction Anxiousness Scale (IAS)	1
Impact of Chronic Skin Disease on Daily Life (ISDL)	1
Private Body Consciousness (PBC)	1
Pharmacoeconomic case report form (PE-CRF)	1
Skindex-16	1
State-Trait Anxiety Inventory (STAI)	1
EQ-5D VAS	1
Quality of life in parents of children with AD questionnaire	1
Family Dermatology Life Quality Index (FDLQI)	1
VAS for awareness of stress and insomnia	1
Profile of Mood States (POMS) score	1
Patients' Global Impression (PGI) 6-step Likert-scale	1
Freiburger Quality of Life Index (FLQA-d)	1
Sickness Impact Profile (SIP)	1
Wu et al quality of life scale	1
Multidimensional Mood Questionnaire (MDMQ)	1
Skindex	1
Skindex-17	1
Child-friendly EQ-5D	1

DLQI,¹⁴⁷ IDQOL,¹⁴⁸ CDLQI,¹⁴⁹ and DFI questionnaire.¹⁵⁰ As noted by Rehal and Armstrong,⁸ there was overlap in the creators of each of these 4 tools, with consequent similarities in their components. Perhaps the most disconcerting trend we found in the use of QOL scales was that 75% of identified instruments were used only once. Continued increases in the reporting of QOL outcomes will be of limited benefit for interstudy comparisons if the diversity of measures used also continues to rise.

Our study has several limitations. First, we reviewed studies published over a defined timeframe

of 5 years, potentially hindering our ability to ascertain trends and between-year comparisons in the use of outcome measures. Nevertheless, our searches yielded >600 records, of which 135 were eligible for review. Despite our studied time period being 20 years shorter than an earlier systematic review on this topic,⁸ the number of RCTs included in our study was over a third of that included in the previous review. Second, we restricted our review to RCTs. It is unclear whether studies with less rigorous methods have similar trends in reporting disease severity and QOL outcomes. The decision to only

include evidence of the highest level was made a priori. Finally, our search strategy did not encompass gray literature (ie, unpublished or generally inaccessible literature). Therefore, we potentially excluded unpublished trials.

Nevertheless, this systematic review highlights the growing variability of measures used to assess disease severity and QOL in RCTs on patients with AD. The resulting heterogeneity of reported outcomes hinders their synthesis and translation to clinical practice. Standardization of disease severity and QOL outcome instruments is essential for comparability among studies and improved quality of research evidence.

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