Assessing Pruritus Among Patients With Atopic Dermatitis: Targeted Literature and Instrument Review

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BACKGROUND

- Pruritus is a key criterion in the diagnosis of atopic dermatitis (AD) and has been associated with lower levels of health-related quality of life (HRQOL) in both pediatric and adult patients.

OBJECTIVE

- The goal of this targeted literature and instrument review was to identify concepts that are potentially relevant for the measurement of pruritus in upcoming clinical trials among adolescent and adult patients with AD.

METHODS

Targeted Literature Review

- Two primary sources were used to generate information for the literature review: the PubMed medical literature database and unpublished ("grey") literature (e.g., meeting abstracts, clinical trials, and practice guidelines).
- A total of 60 English language publications were identified between the years 2000 to 2010, relating to AD and itch (pruritus).
- Among these 60 publications, articles selected for further review included those that reported on the patient perspective and/or the severity, frequency, or impact of AD-related pruritus. A total of 10 articles were included in the literature review.
- Studies were excluded for the following reasons: not an AD population of interest; not specifically measuring itching/pruritus; not specifically addressing characteristics, frequency, severity, or experiences of itching/pruritus; a focus on clinician attitudes (not patient attitudes); a focus on psychometric evaluation of instruments; a focus only on infants or younger children.

Targeted Instrument Review

- To supplement measures identified in the literature, searches of both published patient-reported outcome (PRO) instrument sources (e.g., Patient-Reported Outcome and Quality of Life Instruments Database [PROQOLID]) and RTI-HS's internal PRO instrument repository were conducted to generate a list of potential PRO measures for review.
- Questionnaires were reviewed if they assessed constructs related to the severity, frequency, and/or impact of AD-related pruritus or included constructs that were potentially relevant to the measurement of AD-related pruritus.
- Identified PRO instruments were evaluated based on the criteria described in the Food and Drug Administration's 2009 PRO Guidance.[1]
- Additional desktop research was conducted via the Internet, to obtain basic information on the identified instruments (e.g., use in clinical research, information on development and validation).

RESULTS

Targeted Literature Review

Presentation and Diagnostic Criteria for AD

- AD is one of the most common inflammatory skin diseases and is increasing in prevalence.[2]
- In approximately 70% of cases, AD symptoms begin during infancy or early childhood[3] and tend to follow a chronic or chronically relapsing course.[4]
- AD involves a wide spectrum of dermatological manifestations (i.e., presentation, severity, and distribution).
- The Hanifin and Rajka[5] and UK diagnostic criteria[6] state that the individual must have an itchy skin condition in the last 12 months, as well as three or more criteria relating to the age of onset, flexural involvement, dry skin, other atopic disease, and visible flexural dermatitis.

Characteristics of AD-Related Pruritus

- Pruritus, or itching, is a cardinal symptom of AD[5] and is often one of the first presenting symptoms.[4]
- Itching leads to scratching, which leads to and exacerbates the skin lesions.
  - AD has been referred to as the "itch that rashes."[7]
  - The cycle of itching and scratching is considered an important factor in the maintenance of AD symptoms and is believed to be one of the first symptoms of an impending AD flare.[8]
  - Scratching tends to cause further itching, leading to the so-called "itch-scratch cycle."[4]

Frequency and Duration of AD-Related Pruritus

- It is not uncommon for individuals with AD to experience itching on a daily basis.
  - 28%[9] to 91%[10,11] of AD patients report pruritus on a daily basis.
  - Two-thirds of patients (68%) experience five or more itching episodes per day.[10]
- The duration of itch is prolonged for many patients, with little reprieve from month to month.
  - 41% of patients report a duration of 12 months or more, 27% report a duration of 6 to 12 months, and 32% report a duration of 1 to 6 months.[11]
  - Only a minority of patients report the absence of itch for more than a week or a month at a time.[9]
- Pruritus occurs most often, and with longer duration of itch episodes, in the evening and nighttime hours, as well as during the winter months.
  - In the Yosipovitch et al. study,[11] 65% of patients reported high frequency of itching at night, and 39% reported their nighttime itching to be continuous.
  - Participants in the Dawn et al. study[10] also reported a higher itch frequency at night and in the evening, as well as during the winter.

Intensity of AD-Related Pruritus

- The severity of AD has been associated with more intense pruritus.
  - A study among 22 adult patients with AD in Japan showed that the severity of disease (i.e., skin inflammation) provided a greater contribution than dry skin to the development of pruritus.[12] Prior to this study, dry skin was considered to be a primary cause of pruritus in patients with AD.
- More itch episodes (i.e., increased frequency of itch) have been associated with higher itch intensity.[10]
- Consistent with the frequency of AD-related itch, the intensity of pruritis has been shown to be higher in the evening and nighttime hours.[9]
- The patient-reported "worst" itch intensity was shown as almost twice that of a mosquito bite.[+,11]

Factors Exacerbating AD-Related Pruritus

- Several factors have been reported by patients with AD to exacerbate or trigger AD-related itching.
  - Table 1 summarizes sample characteristics and results of factors that exacerbate or trigger itching.

[+] Itch intensity as expressed by visual analog scale (VAS): at the current moment (now), at the time of worst pruritus, at the time the condition was in the best state, and at the time of the strongest itch after a mosquito bite.

Table 1. Factors That Exacerbate or Trigger Itching in AD

Study Characteristic	Chrostowska-Plak et al., 2009[9] N = 89	Yosipovitch et al., 2002[11] N = 100	Williams et al., 2004[a,2] N = 250
Age in years, mean (SD)	31.6	24.3	Children[b]
Age in years, range	18-60	14-65	12-14
Exacerbating factor			
Skin dryness	89.9%	71%	—
Sweating/sweat from exercise	87.6%	96%	41.8%
Physical effort (activity)	65.0%	73% (55%)	—
Some foods	57.3%	—	—
Hot baths/hot water	55.1%	48%	—
Stress	—	71%	—
Hot weather/heat	—	—	39.1%
Fabrics, especially wool	—	64%	40.0%

SD = standard deviation.
[a] This study asked about factors that made the AD "itchy rash" worse; it was not directed specifically to AD-related pruritus, which may or may not involve a rash.
[b] No mean age reported.

Impact of AD-Related Pruritus

- Patients with AD have described their itching as annoying, unbearable, and bothersome.[10,11]
- Patients attribute a variety of problems to their AD-related pruritus, including difficulty concentrating, decreased sexual desire, and changed eating habits.[11]
- Pruritus has been associated with depression and lower HRQOL among adult patients with AD.[13,14]
  - Results of a study by Reich et al.[13] among patients with AD suggested that itching intensity plays an important role in determining patient psychosocial well-being. A relationship between pruritus and depression also was found.
- AD-related itching also has been associated with lower HRQOL in pediatric patients.
  - In a German study of children (aged 8-12 years) and adolescents (aged 13-18 years) with AD, HRQOL was found to be significantly negatively correlated with itch intensity.[4]
  - In a Chinese study of children with AD (aged 5 to 16 years), 50% reported that their itching negatively affected their HRQOL.[15]
- The phenomenon that itching is often most frequent and intense in the evening or at night also is connected with problems falling asleep or awakening during the night due to itch.
  - Yosipovitch et al.[11] found that 84% of patients had difficulty falling asleep, and 79% were awakened in the night by pruritus.
  - Similarly, Chrostowska-Plak et al.[9] reported that itch caused significant difficulties in falling asleep in 80.9% of patients; 41.6% of individuals reported severe sleeping problems, and 39.3% reported mild sleeping problems.

Targeted Instrument Review

Nine instruments addressing aspects of pruritus were identified for review (Table 2). While some of these instruments were not developed for or among a population with AD (e.g., they may have been developed for patients with chronic itch or plaque psoriasis), they were included in the review to provide a broad view of the various pruritus concepts and items previously developed.

Table 2. PRO Instruments (or Subscales) for Pruritus and AD

Instrument	Purpose	Development Sample and Age	Total Number of Pruritus-Specific Items
Pruritus-specific instruments (not including QOL)			
5-D Itch Scale[16]	Brief, single-page instrument to measure multidimensional aspects of pruritus	Chronic pruritus Ages 8-90 (mean age 48 + 13.8)	8
Chronic Itch Questionnaire[17]	To assess the prevalence and characteristics of itch; also associated factors such as QOL, affect, and extent of itch	Chronic pruritus Ages 21+	16+
Eppendorf Itch Questionnaire[18]	To provide a description of the itch sensation; measuring affective and sensory components (based on the McGill Pain Inventory[26])	AD Ages 17-70	80+
Yosipovitch Itch Questionnaire[11] (investigator administered)	To assess the sensory and affective components of itch (based on the McGill Pain Inventory[26])	AD Ages 14-65	12+
Itch Severity Scale (ISS)[19]	To measure pruritus severity and impact (based on the Yosipovitch Itch Questionnaire)	Plaque psoriasis Ages 18-70	7
Patient Benefit Index, standard version (PBI-S)[20]	To assess patients' treatment needs and benefits in skin diseases, specifically pruritus; uses predefined therapy needs and generates an importance weighted benefit index	Chronic pruritus Ages 19-86	27 needs/ 27 benefits
Pruritus assessment tool[21]	To measure pruritus intensity	Moderate to severe plaque psoriasis Ages 18+	1
AD and pruritus QOL instruments			
ItchyQoL[22]	To measure 3 constructs related to the effects of pruritus on QOL: • Symptoms • Functional limitations • Emotions A pruritus-specific QOL instrument	Urticaria/hives, dermatitis/eczema, other, idiopathic itching Ages 18+	22
Quality of Life Index for Atopic Dermatitis (QoLIAD)[23]	To measure the impact of AD and its treatment on QOL; a needs-based assessment	AD Ages 16+	0

QOL = quality of life.

Instrument Review Summary

- Several of the development or evaluation studies for the reviewed instruments included patients with AD, but among those designed to assess the severity of pruritus (i.e., excluding the PBI-S and HRQOL instruments), only one, the 80+ item Eppendorf Itch Questionnaire, was developed exclusively in an AD population.[†]
  - The 5-D Itch Scale, Chronic Itch Questionnaire, and PBI-S included patients with AD as part of a chronic pruritus population, but the sample of patients with AD was not specified.
  - The ItchyQoL did involve concept elicitation from patients with pruritus from various dermatological conditions, but the validation sample was limited to 29 patients with AD out of the total sample of 89; details regarding the involvement of patients with AD in the qualitative research were not provided.
  - The QoLIAD, designed to measure the impact of AD on HRQOL, was developed and evaluated among patients with AD, but the content is not specific to the impact of pruritus.
- Psychometric evaluation of three of the instruments included patients younger than 18 years, and one of these, the 5-D Itch Scale, included patients younger than 16 years.
- None of the reviewed measures were developed or evaluated with the rigor outlined in the FDA's PRO guidance.

[†] The Yosipovitch Itch Questionnaire is clinician administered and was not psychometrically evaluated.

CONCLUSIONS

- The results of this targeted review indicate the need for new treatments that improve pruritus among both adolescent and adult patients with AD.
- To communicate this treatment benefit, the development of a new AD-related pruritus instrument, which follows the recommended guidelines outlined in the FDA PRO guidance, is warranted to thoroughly assess the effect of therapy on this important disease symptom.

REFERENCES

1. US Department of Health and Human Services. Food and Drug Administration. December 2009. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf. Accessed April 18, 2012.
2. Williams HW, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. J Allergy Clin Immunol. 1999 Jan;103(1 Pt 1):125-38.
3. Williams JR, Burr ML, Williams HC. Factors influencing atopic dermatitis-a questionnaire survey of schoolchildren's perceptions. Br J Dermatol. 2004 Jun;150(6):1154-61.
4. Weisshaar E, Dieppgen TL, Bruckner T, Fartasch M, Kupfer J, Lob-Corzilius T, et al. Itch intensity evaluated in the German Atopic Dermatitis Intervention Study (GADIS): correlations with quality of life, coping behaviour and SCORAD severity in 823 children. Acta Derm Venereol. 2008;88(3):234-9.
5. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol. 1980;(Suppl 92):44-7.
6. Schultz Larsen F, Hanifin JM. Secular change in the occurrence of atopic dermatitis. Acta Derm Venereol Suppl. (Stockh) 1992;176:7-12.
7. McCuaig C. The itch that rashes: an update on atopic dermatitis. Can J Diagnosis. 2003;20:69-76.
8. Pfeifer-Ott B, Godfrey J. Patients report many different signs and symptoms as indicators of impending flare in atopic eczema. J Eur Acad Dermatol Venereol. 2003;17(Suppl 3):181.
9. Chrostowska-Plak D, Salomon J, Reich A, Szepietowski JC. Clinical aspects of itch in adult atopic dermatitis patients. Acta Derm Venereol. 2009;89(4):379-83.
10. Dawn A, Papoiu AD, Chan YH, Rapp SR, Rassette N, Yosipovitch G. Itch characteristics in atopic dermatitis: results of a web-based questionnaire. Br J Dermatol. 2009 Mar;160(3):642-4.
11. Yosipovitch G, Goon AT, Wee J, Chan YH, Zucker I, Goh CL. Itch characteristics in Chinese patients with atopic dermatitis using a new questionnaire for the assessment of pruritus. Int J Dermatol. 2002 Apr;41(4):212-6.
12. Hachisuka J, Takeuchi S, Kido M, Fukiwake N, Furue M. Severity of disease, rather than xerosis, correlates with pruritus in patients with atopic dermatitis. Int J Dermatol. 2009 Apr;48(4):374-8.
13. Reich A, Chrostowska-Plak D, Szepietowski JC. The influence of itching on atopic dermatitis patients' well-being. Acta Derm Venereol. 2007;87(5):471-2.
14. Gupta MA, Gupta AK, Schork NJ, Ellis CN. Depression modulates pruritus perception: a study of pruritus in psoriasis, atopic dermatitis, and chronic idiopathic urticaria. Psychosom Med. 1994 Jan-Feb;56(1):36-40.
15. Hon KL, Leung TF, Wong KY, Chow CM, Chuh A, Ng PC. Does age or gender influence quality of life in children with atopic dermatitis? Clin Exp Dermatol. 2008 Nov;33(6):705-9.
16. Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010 Mar;162(3):587-93.
17. Matterne U, Strassner T, Apfelbacher CJ, Diepgen TL, Weisshaar E. Measuring the prevalence of chronic itch in the general population: development and validation of a questionnaire for use in large-scale studies. Acta Derm Venereol. 2009;89(3):250-6.
18. Darsow U, Scharein E, Simon D, Walter G, Bromm B, Ring J. New aspects of itch pathophysiology: component analysis of atopic itch using the "Eppendorf Itch Questionnaire." Int Arch Allergy Immunol. 2001 Jan-Mar;124(1-3):326-31.
19. Majeski CJ, Johnson JA, Davison SN, Lauzon CJ. Itch Severity Scale: a self-report instrument for the measurement of pruritus severity. Br J Dermatol. 2007 Apr;156(4):667-73.
20. Blome C, Augustin M, Siepmann D, Phan NQ, Rustenbach SJ, Ständer S. Measuring patient-relevant benefits in pruritus treatment: development and validation of a specific outcomes tool. Br J Dermatol. 2009 Nov;161(5):1143-8.
21. Gottlieb A, Feng J, Harrison DJ, Globe D. Validation and response to treatment of a pruritus self-assessment tool in patients with moderate to severe psoriasis. J Am Acad Dermatol. 2010 Oct;63(4):580-6.
22. Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot quality-of-life instrument for pruritus. J Am Acad Dermatol. 2008 Aug;59(2):234-44.
23. Whalley D, McKenna SP, Dewar AL, Erdman RA, Kohlmann T, Niero M, et al. A new instrument for assessing quality of life in atopic dermatitis: international development of the Quality of Life Index for Atopic Dermatitis (QoLIAD). Br J Dermatol. 2004 Feb;150(2):274-83.
24. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain; 1975. p. 277-99.

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