Research Techniques Made Simple: Itch Measurement in Clinical Trials

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Chronic itch, defined as itch lasting longer than 6 weeks, is a highly prevalent and debilitating symptom known to profoundly and negatively affect quality of life. The development of effective targeted therapies for some chronic itch disorders such as atopic dermatitis has given widespread recognition to the importance of measuring itch in clinical trials. Clinical trials now use itch measurement as a primary outcome measure, and steps toward the standardization of itch assessment are being made to meet the growing need for reliably measuring itch and its impact on quality of life in the clinical research setting. Itch can be evaluated via subjective patient-reported assessments or by objective measurement of scratching activity and scratching-induced skin changes. Herein, methods for the subjective assessment of itch via both unidimensional and multidimensional tools are discussed.

INTRODUCTION

Pruritus or itch was defined in the late 17th century by the German physician Samuel Hafenreffer as an “unpleasant sensation that elicits the desire or reflex to scratch” (Ikoma et al., 2006, pp. 535). Although scratching in response to acute itch may be protective against insects, parasites, and noxious environmental substances, in its chronic form, itch is almost always pathologic. Defined as itch lasting longer than 6 weeks, chronic itch affects approximately 15% of the overall population and has a profoundly negative impact on QoL, quality of life.

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Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; NRS, numerical rating scale; PBI-P, Patient Benefit Index for Pruritus; PRO, patient-reported outcome; QoL, quality of life; VAS, visual analogue scale; VRS, verbal rating scale

Dramatic advances in the treatment of chronic itch, or itch lasting longer than 6 weeks, have increased the need for itch evaluation in the clinical research setting.

- Itch can be evaluated via subjective patient-reported assessment of itch intensity (e.g., numerical rating scale, visual analogue scale) or by objective measurement of scratching activity and scratching-induced skin changes (e.g., actigraphy, physician assessment).
- Itch is a complex, multifactorial entity with profound effects on quality of life. Therefore, multidimensional assessments of patient well-being (e.g., ItchyQoL) provide valuable information.
- Current limitations of subjective measures of itch include the need for optimization and further delineation of a clinically meaningful level of improvement. Objective measurement of itch is promising but currently requires cautious interpretation.

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improvement of at least 4 points in peak NRS score at weeks 2, 4, and 16 or of at least 3 points at week 16 in the weekly average of daily peak NRS scores (Simpson et al., 2016). Emerging studies using various unidimensional itch intensity scales are allowing refinement of which endpoints and milestones translate to clinically meaningful patient outcomes.

Although unidimensional itch intensity scales have been used successfully in many clinical trials, potential limitations exist. First, given that these tools require patients to recall itch intensity over a given period, typically 24 hours, there is vulnerability to environmental and psychosocial confounders present at the time of recording. Second, what recall period is ideal for effectively measuring itch has not been clearly defined. Third, some investigators and/or patients may use average versus peak itch intensity, which can have different levels of sensitivity and specificity in measuring itch. To this point, in a recent clinical trial using the neurokinin 1 receptor antagonist traladipitan in chronic itch secondary to AD, VAS measurement of peak/worst itch intensity achieved significance, but mean itch intensity did not. Fourth, the time of day at which itch is measured may also affect itch severity. In the same clinical trial with traladipitan for AD, worst NRS itch during the day did not reach significance, but NRS itch at night did (Heitman et al., 2018). Fifth, missing data are another concern. In a large validation study of 471 patients, 12.5% of patients failed to record itch intensity on the VAS at the first time point compared with 4.2% and 7.2% with NRS and VRS, respectively. Notably, patients older than 60 years showed nearly double the number of missing values on the VAS and NRS (16.1% and 9.1%, respectively) compared with younger participants. The VRS had the lowest number of missing values in elderly patients with a rate of 3.7% at the first time point (Phan et al., 2012). Difficulty with the VAS and NRS may be due to the more abstract nature of converting a subjective sensation to a specific mark or number on a spectrum. However, methods such as daily diaries can be used to maximize data points and to minimize variability, issues with recall, and missing data. Patient education before use is important to ensure proper documentation and usage (Phan et al., 2012). A cartoon-illustrated version of the 11-point NRS, called the ItchyQuant, showed concurrent validity, was preferred by patients and may be easier to use than the traditional NRS (Haydek et al., 2017) (Figure 2).

### MULTIDIMENSIONAL ITCH ASSESSMENTS

Multidimensional scales have been designed to obtain a more holistic picture of the burden of itch on patients, taking into account measures of QoL, itch frequency, course, and/or patient expectations. These include the Dermatology Life Quality Index (DLQI), ItchyQoL, 5-D Itch Scale, and Patient Benefit Index for Pruritus (PBI-P) (Blome et al., 2009; Desai et al., 2008; Elman et al., 2010; Finlay and Khan, 1994; Phan et al., 2012; Reich et al., 2012).
Pereira and Stander, 2017) (Table 1). Patient QoL (e.g., sleep, social functioning) is profoundly affected by chronic itch and is increasingly measured in clinical trials (Kini et al., 2011). Although validated scales such as the DLQI use itch as a component in its overall scoring, it is not designed to specifically capture the relationship of itch to QoL. The DLQI is therefore often used as a QoL measurement in conjunction with unidimensional itch scales. The DLQI is a brief 10-item questionnaire in which patients rate nonspecific skin symptom (itchy, sore, painful, stinging) severity and disease impact on various aspects of daily life and social functioning scored from 0 to 3 (0 = not at all, 1 = a little, 2 = a lot, 3 = very much). It is available in many languages and in a children’s version. The DLQI predominantly emphasizes skin appearance and its impact on daily functioning, making it less applicable to itch without skin manifestations, and does not directly assess psychological burden (Lewis and Finlay, 2004). To address these concerns, ItchyQoL, an itch-specific, 22-item questionnaire, was developed. Although more time consuming than the DLQI, ItchyQoL is highly tailored to patients experiencing itch and better evaluates psychological burden (e.g., frustration, irritability) (Desai et al., 2008; Pereira and Stander, 2017; Stumpf et al., 2018). ItchyQoL addresses three domains of itch impact, symptoms, function, and emotions, with each item scored from 1 to 5 (1 = never; 2 = rarely; 3 = sometimes; 4 = often; 5 = all of the time) (Desai et al., 2008). Thus, by coupling itch intensity directly to various aspects of QoL, the ItchyQoL provides a more comprehensive assessment of patients suffering from chronic itch. Indeed, validation in patients with chronic itch disorders of multiple different causes showed construct validity and reproducibility (Desai et al., 2008).

An additional important component in understanding the impact of itch on an individual is time. Although the intensity or quality of one’s itch can be captured at one point in time, understanding the natural time course and rapidity of response to treatment can also yield insight into the impact of itch on patients. The 5-D itch scale assesses itch course over a 2-week period with consideration of patients’ perspective on their symptoms. The five dimensions are degree (5-point NRS), duration (total hours), direction (better or worse), disability (impairment of sleep, leisure, and function at home/ work), and distribution on skin (16 potential locations of itch) (Elman et al., 2010). A study of 234 patients with itch of multiple causes found the 5-D itch scale assesses itch course and QoL impact while remaining brief, easy to use, and widely applicable.

The PBI-P is a tool that uniquely evaluates treatment response in the context of patient-specified goals of therapy. Before treatment, patients complete a questionnaire to determine the value placed on 27 potential benefits from treatment (e.g., reduced itch, improved sleep), ensuring that the morbidities associated with itch that are most important to each patient are measured. After treatment, patients complete a questionnaire on the outcome of the 27 potential benefits. A weighted score is then calculated based on pre- and post-treatment responses (Blome et al., 2009). PBI-P validation in 100 patients with chronic itch showed good correlation with...
the VAS and DLQI (Blome et al., 2009). Although time consuming, the PBI-P provides valuable insight into how patients’ expectations play into their perceptions of treatment. These multidimensional assessments each provide unique insights into chronic itch symptomatology and impact, and they differ in terms of the kinds of data that they will generate.

**Electronic Diaries**

Monitoring itch intensity and/or QoL over time, particularly with respect to therapeutic interventions, is a critically important aspect of clinical trials. Such measurements can be performed as infrequently as predefined study visits scheduled weeks to months apart or as frequently as multiple times per day. If data are obtained inconsistently, measured at the wrong times, or simply missing, then the outcomes can be greatly affected. Electronic diaries (eDiaries) are increasingly used in clinical trials to record patient responses to various itch measurement tools. In addition to simplifying data entry and increasing patient compliance through reminders, eDiaries track the exact time when patients enter information, a notable benefit over paper-based diaries in which patients may retroactively respond to questions from missed time points. The eDiary modules can be accessed on tablets given to patients or, increasingly, via smartphone applications such as ItchApp (Arone, Saint-Maur des Fosses, France), which can be used on smartphones and has been validated (Gernart et al., 2017; Schnitzler et al., 2018) (Table 1). eDiaries can improve accuracy by minimizing recall bias and missing data and increasing the number of data points. Monitoring has also been successfully facilitated through the integration of itch assessments into electronic medical records (Mollanazar et al., 2016).

**Assessment of Scratching Activity**

Although itch is, by definition, a subjective sensation, scratching is an objective event. Given that scratching is a virtually unavoidable reflex in response to itch, it can be measured in an objective fashion, such as actigraphy or physician assessment, to further assess chronic itch symptoms in patients. Indeed, investigator-based measurements for AD disease severity including the Eczema Area and Severity Index (i.e., EASI) and Scoring Atopic Dermatitis (i.e., SCORAD) tools measure scratching-induced changes in the skin as a part of the overall assessment. Furthermore, scratching severity assessment tools show potential in validation studies and may be particularly helpful in pediatric populations in which PROs are harder to obtain than in adults (Udkoff and Silverberg, 2018). However, although objective measures add additional information, how scratching activity, and thus lesion development, relates to QoL remains to be more clearly defined. For example, patients with AD typically exhibit excoriations, whereas individuals with idiopathic forms of itch often do not exhibit secondary lesions despite even higher mean itch severity (Oetjen et al., 2017). Additionally, patients with severe itch may practice avoidance techniques, and others may scratch out of habit, even in the absence of itch sensation or burden as in primary excoriation disorders (Stander et al., 2013). How objective measurements of scratching activity add to current subjective metrics is an exciting area of research with current data requiring cautious interpretation.

**Multiple Choice Questions**

1. Which unidimensional itch intensity scale allows patients to mark itch intensity on a spectrum depicted as a 10-cm ruler—shaped line labeled at each end with 0 for no itch and 10 for worst imaginable itch?
   A. Verbal rating scale (VRS)
   B. Visual analogue scale (VAS)
   C. Numerical rating scale (NRS)
   D. Dermatology Life Quality Index (DLQI)

2. Patient ease of use and compliance with the unidimensional itch intensity scales can be improved by which of the following?
   A. Electronic diaries (eDiaries)
   B. Patient education before use
   C. Cartoon-illustrated versions
   D. All of the above

3. The impact of itch on patient quality of life (QoL) can be assessed by which of the following tools?
   A. Visual analogue scale (VAS)
   B. ItchyQoL
   C. Eczema Area and Severity Index (EASI)
   D. Scoring Atopic Dermatitis (SCORAD)

4. In addition to itch intensity alone, multidimensional itch assessments may also evaluate which of the following?
   A. Patient QoL
   B. Itch frequency and course
   C. Patient expectations and treatment goals
   D. All of the above

5. Which of the following are superior tools for the measurement of itch?
   A. Unidimensional itch intensity scales
   B. Multidimensional itch assessments
   C. Objective tools that measure scratching activity and associated skin changes
   D. None of the above

**Conclusions**

Dramatic advances in the treatment of chronic itch disorders have increased the need for itch evaluation in the clinical research setting. The unidimensional itch intensity scales (e.g., NRS, VRS, and VAS) provide simple, reliable, and valid measures of itch intensity that have successfully been used in large-scale clinical trials. However, itch is a complex and multifactorial entity that profoundly and negatively affects QoL. Thus, increasingly, QoL assessments, such as the DLQI, or multidimensional tools that incorporate QoL, such as the ItchyQoL, 5-D, and PBI-P, show great potential for more holistically capturing the impact of itch. New apps and tools...
may greatly improve compliance and provide more objective measurements of itch in the future. Ultimately, clinical itch research has emerged as a well-recognized and important area of dermatology. The development of new tools will undoubtedly better inform clinical trials but also directly improve our basic understanding of chronic itch.

CONFLICT OF INTEREST

BSK has worked as a consultant for AbbVie, Concert Pharmaceuticals, Incyte, Menlo Therapeutics, and Pfizer and served on advisory boards for Celgene, Kiniksa Pharmaceuticals, Menlo Therapeutics, Regeneron Pharmaceuticals, Sanofi, and Theravance Biopharma. BSK is also a stockholder of Gilead Sciences and Mallinckrodt Pharmaceuticals and is founder and chief scientific officer of Nuogen Pharma. SE states no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

REFERENCES


DETAILED ANSWERS

1. Which unidimensional itch intensity scale allows patients to mark itch intensity on a spectrum depicted as a 10-cm ruler—shaped line labeled at each end with 0 for no itch and 10 for worst imaginable itch?

Correct answer: B. VAS

The unidimensional itch intensity scales (VAS, NRS, and VRS) provide a simple, reliable, and valid measure of patient-reported itch severity over a given recall period. On the NRS, patients score intensity from 0 (no itch) to 10 (worst imaginable itch), and on the VRS, five descriptions of intensity are selected from 0 (no itch) to 4 (very severe itch).

2. Patient ease of use and compliance with the unidimensional itch intensity scales can be improved by which of the following?

Correct answer: D. All of the above

Ease of use may be a concern in patients with cognitive limitations. These patients may have difficulty with the VAS and NRS because of the abstract thought required to convert a subjective sensation to a line or number. Cartoon-illustrated versions of these scales, such as ItchyQuant, may simplify use, and patient education before use is recommended. Electronic diaries (eDiaries) simplify data entry, increase patient compliance, and ensure that recorded time points are accurate.

3. The impact of itch on patient quality of life (QoL) can be assessed by which of the following tools?

Correct answer: B. ItchyQoL

The 22-item ItchyQoL may be more applicable to patients experiencing itch without skin manifestations and better evaluate for psychological strain (e.g., frustration, irritability). The VAS, EASI, and SCORAD do not measure QoL.

4. In addition to itch intensity alone, multidimensional itch assessments may also evaluate which of the following?

Correct answer: D. All of the above

Multidimensional assessments have been designed to obtain a more holistic picture of the burden of itch on patients. These include the Dermatology Life Quality Index (DLQI), ItchyQoL, 5-D Itch Scale, and Patient Benefit Index for Pruritus (PBI-P).

5. Which of the following are superior tools for the measurement of itch?

Correct answer: D. None of the above

Both subjective and objective measures of itch severity and QoL impact play important and complementary roles in itch assessment. Although unidimensional itch intensity scales are currently the most commonly used in clinical trials, whether they are truly the criterion standard remains to be determined in the future comparative studies.