



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.

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Description: This article, designed for dermatologists, residents, fellows, and related healthcare providers, seeks to reduce the growing divide between dermatology clinical practice and the basic science/current research methodologies on which many diagnostic and therapeutic advances are built.

Objectives: At the conclusion of this activity, learners should be better able to:

- Recognize the newest techniques in biomedical research.

- Describe how these techniques can be utilized and their limitations.

- Describe the potential impact of these techniques.

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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

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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

SUMMARY POINTS

- 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.

quality of life (QoL) (Kini et al., 2011; Stander et al., 2010). The elderly population has an estimated chronic itch prevalence of up to 25% (Standar et al., 2010; Valdes-Rodriguez et al., 2015). Dermatologic disorders such as allergic contact dermatitis, atopic dermatitis (AD), cutaneous T-cell lymphoma, prurigo nodularis, and psoriasis are commonly associated with chronic itch. Chronic itch can also arise in the context of kidney, liver, and neurologic disorders, as well as a variety of hematologic and lymphoproliferative disorders such as polycythemia vera, leukemias, lymphomas, and other malignancies. Many patients present with chronic idiopathic pruritus or pruritus of unknown origin (Millington et al., 2018). Given its high prevalence, association with multiple medical disorders, and highly debilitating nature, there is a great need for medications specifically for chronic itch. To better understand and quantify chronic itch in clinical trials, effective and validated tools are needed, and steps toward the standardization of itch measurement in clinical trials are being taken by groups such as the European Network on Assessment of Severity and Burden of Pruritus (PruNet) (Schoch et al., 2017; Stander et al., 2016).

Recent therapeutic advances that have been tested in randomized clinical trials and in the community have led to dramatic improvements in disease severity in classical chronic itch disorders like moderate-to-severe AD (Beck et al., 2014; Ruzicka et al., 2017; Simpson et al., 2016). These advances have improved the QoL of individuals with AD and placed priority on addressing chronic itch as a central morbidity in AD and other disorders. Although historically used as a secondary endpoint, recent clinical trials have begun to address chronic itch as a primary endpoint (Ruzicka et al., 2017; Yosipovitch et al., 2018b). Thus, in the near future, chronic itch may formally emerge as a primary indication and morbidity, rather

than a secondary medical problem. The focus of this article will be on highlighting new and existing tools that measure itch in patients. This article is not meant to be comprehensive, because the number of metrics for evaluating itch is rapidly increasing, but will highlight some of the most commonly used tools and their various strengths and weaknesses in advancing clinical itch research.

UNIDIMENSIONAL ITCH INTENSITY SCALES

Unidimensional scales measure a single variable such as pain or itch intensity alone and have recently been adapted to measure itch intensity for clinical trials (Phan et al., 2012). Subjective unidimensional scales have been well validated, are effective, and are widely used in pain research (Hjemstad et al., 2011). These include the numerical rating scale (NRS), verbal rating scale (VRS), and visual analogue scale (VAS) (Table 1). On the NRS, patients score itch intensity on a scale from 0 (*no itch*) to 10 (*worst imaginable itch*) over a period of time, typically 24 hours (Figure 1a). On the VRS, patients score itch intensity using five categories from *no itch* (0) to *very severe itch* (4) (Figure 1b). The VAS is a continuous visual scale that 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* (Phan et al., 2012) (Figure 1c). Additional itch severity assessments have been developed and validated, such as the severity of pruritus scale (Yosipovitch et al., 2018a). Collectively, these unidimensional scales are simple and efficient tools for measuring subjective itch intensity.

Two studies with 471 and 310 patients with chronic itch of different etiologies showed the NRS, VRS, and VAS to be reliable with high concordance (Phan et al., 2012; Reich et al., 2012). The NRS was a key secondary endpoint to measure itch in patients with moderate-to-severe AD in pivotal phase 3 clinical trials leading to the approval of dupilumab, an anti-IL-4 receptor α monoclonal antibody, in 2017 (Simpson et al., 2016). Similarly, the VRS was used as a secondary endpoint, whereas the VAS was used as a primary endpoint, to measure itch in patients with moderate-to-severe AD in phase 2 clinical trials for nemolizumab, an anti-IL-31 receptor A monoclonal antibody (Ruzicka et al., 2017). Nemolizumab showed dose-dependent, anti-itch efficacy in these studies. Taken together, recent clinical trials in AD have shed light on how metrics for itch can be successfully used to monitor the efficacy and utility of new and emerging treatments.

In addition to quantifying itch, defining clinically meaningful improvements in itch intensity, or any patient-reported outcome (PRO), allows for both investigators and clinicians to understand how much of an impact a given medication may actually have on the patient's itch severity as described in the SPIRIT-PRO Extension (Calvert et al., 2018). In other words, a statistically significant improvement in itch may not equate to a clinically meaningful improvement in itch. Based on investigator-reported and PRO data from four clinical trials in plaque psoriasis, a 4-point change in the NRS was recommended as a clinically meaningful improvement via anchor- and distribution-based methods (Kimball et al., 2016). Alternatively, a 2–3-point decrease in both VAS and NRS was suggested as the minimal clinically important difference after an observational study that included patients with chronic itch of multiple causes (Reich et al., 2016). The clinical trials for dupilumab used an

Table 1. Summary of Measurement Tools for Itch Intensity, Associated Symptoms, and Quality of Life

Scale	Description	Strengths	Limitations	Validation
Unidimensional Itch Intensity Scales				
NRS	Intensity rated 0–10	Simple to use	No context at the time of measurement	Phan et al. (2012) Reich et al. (2012)
VRS	Intensity rated from <i>none</i> (0) to very severe (4)	Validated and reliable Widely applicable	(e.g., environmental confounders) Recall bias	
VAS	Intensity marked on 10-cm line labeled 0–10	Easily assessed over time	Missing data	
Multidimensional Itch and Quality of Life Assessments				
DLQI	10-item questionnaire rating nonspecific symptom severity and disease impact on daily functioning Items scored as 0 = <i>not at all</i> , 1 = <i>a little</i> , 2 = <i>a lot</i> , 3 = <i>very much</i>	Simple to use Validated and reliable Available in many languages and a children’s version Can be directly compared with other dermatologic conditions	Mildly time consuming Not itch specific Less applicable to itch without skin manifestations Psychological burden not directly assessed	Lewis and Finlay (2004)
ItchyQoL	22-item questionnaire addressing three domains of itch impact: symptoms, function, and emotions. Items scored as 1 = <i>never</i> , 2 = <i>rarely</i> , 3 = <i>sometimes</i> , 4 = <i>often</i> , 5 = <i>all of the time</i>	Simple to use Validated and reliable Highly itch specific Psychological burden assessed	Moderately time consuming Difficult to get multiple time points	Desai et al. (2008)
5-D	Recall over past 2 weeks: Duration (total hours) Degree (5 point NRS) Direction (better or worse) Disability (QoL) Distribution	Simple to use Validated and reliable Evaluates symptom change over time Itch specific	Moderately time consuming Recall bias	Elman et al. (2010)
PBI-P	27 potential treatment benefits weighted by patient preference	Patient treatment goals and expectations accounted for Itch specific	Significantly time consuming	Blome et al. (2009)
Electronic Diaries				
ItchApp	Smartphone application currently available for Android phones	Simple to use Validated and reliable High patient compliance Minimizes recall bias	Requires patients to own and operate smartphones	Gernart et al. (2017)

Abbreviations: 5-D, 5-D Itch Scale; DLQI, Dermatological Life Quality Index; NRS, numerical rating scale; PBI-P, Patient Benefit Index for Pruritus; QoL, quality of life; VAS, visual analogue scale; VRS, verbal rating scale.

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 tradipitant 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 tradipitant 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;

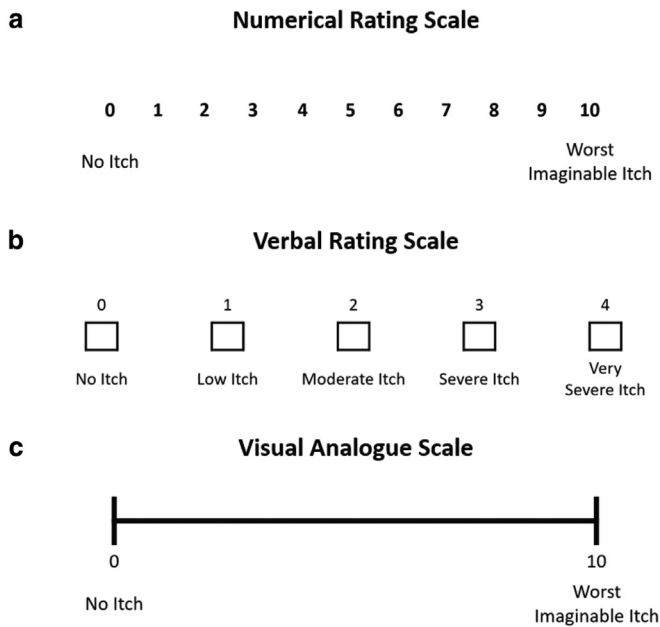


Figure 1. Numerical rating scale, verbal rating scale, and visual analogue scale.

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 to be reliable and valid with high correlation to the unidimensional VAS (Elman et al., 2010). The 5-D itch scale provides valuable information on 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

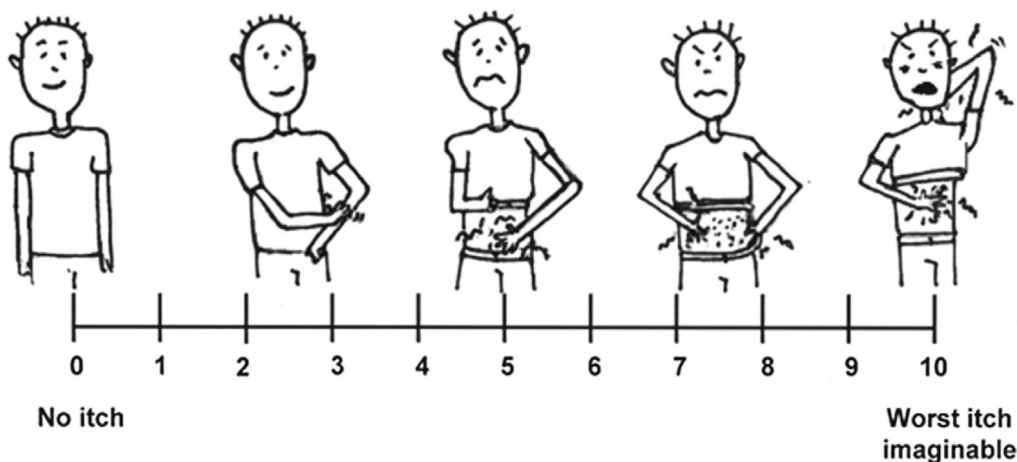


Figure 2. ItchyQuant, an illustrated numeric rating scale for itch severity. Reprinted from Haydek et al. (2017).

RESEARCH TECHNIQUES MADE SIMPLE

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.

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RESEARCH TECHNIQUES MADE SIMPLE

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.