Patient-Reported Outcomes in Onychomycosis: A Review of Psychometrically Evaluated Instruments in Assessing Treatment Effectiveness

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Keywords

Nail diseases · Nails · Onychomycosis · Patient-reported outcomes · Psychometrics · Quality of life · Questionnaires

Abstract

Purpose: Onychomycosis is the most common nail disorder and causes morbidity and impaired quality of life (QOL). Patient-reported outcomes (PRO) are patients' assessment of their health status or treatment response. PROs help assess what is most bothersome to patients to identify targets for intervention. We sought to review the PRO instruments currently used to assess QOL and treatment response in onychomycosis patients. **Procedures:** A systematic review was performed by searching PubMed, Embase, CINAHL, and PsycINFO databases through December 31, 2016, to identify all English language literature on onychomycosis, PRO, and QOL. **Results:** Currently, 5 validated PRO instruments exist specifically for onychomycosis. Oral therapies were most extensively studied using PRO instruments. QOL data generally correlated with clinical change, although patients sometimes reported improvement without any clinically significant nail clearance. The only psychometrically validated PRO instrument used to evaluate treatment response is the OnyCOE-tTM. **Conclusions:** Clinicians may underestimate the impact of onychomycosis on patients. With recent initiatives from health-care management organizations to improve pa-

tient experience and the recent approval of expensive and nonsuperior topical antifungal medications, PROs will be increasingly important in onychomycosis to assess patient priorities and optimize treatment. Future research should evaluate these instruments in special populations and fingernail disease.

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Introduction

Onychomycosis is the most frequent nail disorder, accounting for 50–60% of nail pathology [1], with toenail disease being about 10 times more common than fingernail disease [2]. Onychomycosis affects over 4% of people in North America and Europe and imposes a substantial economic burden [1, 3]. As a disease with mostly benign clinical features, the impact of onychomycosis on patients' quality of life (QOL) is often underestimated. Nail abnormalities can lead to pain, discomfort, limited dexterity and mobility in daily activities [4], and onychomycosis may also be complicated by skin and soft tissue infections [5]. Psychosocial consequences such as embarrassment, decreased self-esteem, anxiety, and depression are often more common in onychomycosis patients than physical sequelae [4, 6].

Patient-reported outcomes (PRO) refer to patients' assessment of their health status or impression of a treatment. Such measurements provide quantifiable data regarding disease impact apart from objective clinical measures. PROs can highlight the most bothersome aspects of onychomycosis for patients and identify targets for intervention [7], thus allowing for the customization of care around patients' goals, treatment optimization, and monitoring of disease activity during therapy [8]. PROs are increasingly becoming an outcome parameter in clinical studies as well as in health-care management and reimbursement [8]. General health questionnaires have limited utility as they are unable to reliably identify problems experienced by dermatologic patients [9]. Instead, disease-specific PRO instruments have been created, validated, and used for onychomycosis.

This review will summarize the current tools used to assess QOL and responsiveness to treatment in onychomycosis patients. First, the 5 current psychometrically validated PRO instruments specific for onychomycosis will be reviewed with a brief discussion of nonvalidated or nonspecific metrics. Then, the use of PROs in evaluating onychomycosis treatment will be discussed.

Methods

We searched PubMed, Embase, CINAHL, and PsycINFO databases for all published, English language, clinical studies using PRO instruments for onychomycosis through December 31, 2016. Search terms included *onychomycosis*, *patient-reported outcomes*, and *quality of life*. All articles using any PRO instrument to evaluate QOL of onychomycosis patients were included, regardless of study design. While some studies evaluated QOL in onychomycosis patients using nonvalidated or nonspecific tools, we emphasized psychometrically evaluated PRO instruments in our discussion. Articles that studied nail or foot pathology in general and failed to separate onychomycosis from other pathology were excluded. Bibliographies were searched for additional studies that met inclusion and exclusion criteria. Of 168 articles, 25 unique studies with an aggregate of 12,821 patients met the inclusion criteria. Quality of evidence was graded on a scale of 1–5 per the Oxford Center for Evidence-Based Medicine levels of evidence. Because of the poor quality of evidence, we were unable to complete a quantitative review and thus present our findings qualitatively.

Results

Of 168 results, 25 unique studies met the inclusion criteria. Eight studies describe baseline characteristics of onychomycosis patients using PRO instruments [10–17], while 8 other studies use nonvalidated instruments or in-

struments nonspecific to onychomycosis (Table 1) [7, 18–25]. Ten studies used PRO instruments to evaluate onychomycosis treatments (Table 2) [26–35].

PRO Instruments

Data collected with PRO instruments are not meaningful without extensive psychometric evaluation; the aspects of this validation are summarized in Table 3. To date, 5 onychomycosis-specific PRO instruments have been validated and are described in Table 4. Overall, all 5 instruments fulfill psychometric validation. Earlier questionnaires contained a generic core of general physical and mental health questions [10, 12, 15], whereas later instruments consist only of disease-specific items [16, 17], which address symptoms, physical functioning, and psychosocial impact particular to onychomycosis. Multiple nonvalidated PRO instruments have been reported, wherein rationale for item selection and psychometric evaluation were absent [18–23].

Lubeck et al. [10, 18] produced the first instrument measuring QOL in onychomycosis patients, the Onychomycosis QOL Questionnaire, which was later revised and validated in patients with toenail onychomycosis. In the validation study for the Lubeck instrument [10], patients with clinical improvement demonstrated statistically significant change in most disease-specific scales over time, whereas no significant change was noted in clinically stable patients, reflecting responsiveness of disease-specific measures.

Turner and Testa [15] later created the Onychomycosis Disease-Specific Questionnaire (ODSQ), which derives questions from the Lubeck instrument and has been validated for both toenail and fingernail disease. The OnyCOE-t™ instrument is another questionnaire developed and modified from the Lubeck instrument [16]. When comparing OnyCOE-t™ scores after treatment with baseline, the clinically improved group of subjects had statistically significant change in all domains including symptom frequency and bothersomeness, physical activities problems, appearance problems, and stigma. However, the clinically unimproved group also had significant changes for 5 out of 7 domains. Uniquely, clinical meaningfulness was evaluated by estimating the minimally clinical important difference (MCID), i.e. how much a scale needs to change to reflect a corresponding clinical change. The authors found that an 8.5-point change on their 100-point scale corresponded to a 25% improvement in nail clearance. The MCID allows physicians to correlate clinical findings with PRO data. Weaknesses include lack of variability or test-retest evaluation

Table 1. Summary of PRO instruments for onychomycosis QOL evaluation

First author [Ref.], year	Study design (patients, n)	PRO Instrument (questions, n)	PRO outcomes	Limitations	QOE
Lubeck [18], 1993 Lubeck [19], 1998	Case control, cross-sectional (299)	Nonvalidated, OM-specific: validated generic core (National Health Interview Survey, Mental Health Index from the MOS, Fleming Self-Esteem Scales) and nonvalidated disease-specific items (55)	Generic health questions were less sensitive than disease-specific questions <i>Concerns:</i> physical appearance (time/pain involved with nail care, embarrassment, self-consciousness, concern with concealing nails), disease symptoms (pain, thickening, discoloration, deformity), and functional limitations associated with standing on one's feet or working with one's fingers <i>Factors NOT affecting QOL:</i> disease site <i>Treatment:</i> 79% asked providers about treatment, but 26% said providers discouraged them from taking medication; 88% were willing to take a drug with short-term side effects, 41% would take such a drug even with the risk of recurrence; 13% were willing to take a drug with long-term side effects	Nonvalidated PRO instrument, control group dissimilar in terms of gender and age, recall bias, selection bias	4
Whittam [20], 1997	Case control, cross-sectional (60)	<i>Nonvalidated, OM-specific:</i> questions based on responses of a pilot group of 20 patients with OM (9)	<i>Main concerns:</i> nail care, pain, footwear limitations <i>Economic burden:</i> OM patients spent more money on nail care and made more visits to clinicians	Nonvalidated PRO instrument, small sample size, confounded by subjects without OM, recall bias, selection bias	4
Schein [21], 1997	Case series (150)	<i>Nonvalidated, OM-specific:</i> generic core (physical functioning, social functioning, pain, health distress, stigma) and disease-specific (symptoms, physical activities) questions (NR)	<i>Main concerns:</i> embarrassment (67%), discomfort (54%), footwear limitations (40%), pain (36%) <i>Factors worsening QOL:</i> female gender <i>Provider differences:</i> dermatologists were more likely to order diagnostic tests and prescribe oral antifungals than podiatrists; podiatrists were more likely to debride	Nonvalidated PRO instrument, no mycological confirmation of OM, small sample size, no control group, nonstandardized treatment, recall bias, selection bias	4
Elewski [22], 1997	Cross-sectional (93)	<i>Nonvalidated, OM-specific:</i> disease-specific questions about physical disease and psychosocial state (15)	92% reported negative psychosocial and/or physical effects <i>Main concerns:</i> nail care (75%), negative self-image (44%), pain (41%), transmission to others (31%), feeling conspicuous (28%), avoiding public facilities (18%) <i>Factors worsening QOL:</i> Duration of disease (≥ 10 years), number of nails involved (≥ 5 nails) <i>Treatment:</i> 66% wanted to continue treatment even if results would be disappointing	Nonvalidated PRO instrument, small sample size, no control group, recall bias, selection bias	4
Drake [23], 1998	Cross-sectional (258)	<i>Nonvalidated, OM-specific:</i> disease-specific questions (patient, physical and functional, psychosocial, and economic domains) based on authors' experience, pilot study, and instrument by Lubeck et al. [18] (57)	70% consider OM at least a moderate problem <i>Main concerns:</i> nail care (76%), embarrassment (75%), pain (48%), pressure (40%), discomfort wearing shoes (38%), picking up small objects (41%) <i>Factors worsening QOL:</i> female gender, fingernail involvement <i>Economic burden:</i> in a 6-month period, there were 58 OM-related sick days and 468 medical visits (1.8 per subject) <i>Treatment:</i> 97% stated they would be willing to pay for a medication with an 80% cure rate, even if their insurance did not cover the cost; 57% would be willing to pay if cure rate was 35%	Nonvalidated PRO instrument, no control group, unclear how subjects were diagnosed, recall bias, selection bias	4
Drake [12], 1999	Cross-sectional (532)	<i>Validated, OM-specific:</i> generic core (MOS Short Form Survey, Positive Well-Being scale from Psychological General Well-Being Index) and disease-specific questions (social, emotional, symptoms) in English, German, French, and Italian (40 for toenail, 47 for fingernail)	Generic health questions were less sensitive than disease-specific questions <i>Main concerns:</i> embarrassment, work functioning, decreased social activity, fear of spread, and pain Physicians tended to underestimate pain <i>Factors worsening QOL:</i> female gender, older age, fingernail involvement, duration of disease, number of nails involved, proportion of individual nails involved <i>Cultural differences:</i> German and US patients felt more seriously affected by OM than Italian patients	No control group, unclear how subjects were diagnosed, recall bias, selection bias	4
Lubeck [10], 1999	Case series (129)	<i>Validated, OM-specific:</i> generic core (Medical Outcomes Study: general health perceptions, pain, mental health, social function, health distress, physical function, health transition) and disease-specific questions (toe symptom frequency and bothersomeness, problems with appearance, problems with activities, stigma, treatment satisfaction) (80)	Generic health questions were less sensitive than disease-specific questions <i>Factors worsening QOL:</i> female gender	Small sample size, no control group, no mycological confirmation of diagnosis, recall bias, selection bias	4

Table 1 (continued)

First author [Ref.], year	Study design (patients, n)	PRO Instrument (questions, n)	PRO outcomes	Limitations	QOE
Lubeck [11], 1999	Case series (113)	<i>Validated, OM-specific:</i> questionnaire developed by Lubeck et al. [18, 19]	<i>Provider differences:</i> improvements in QOL were greater in the group treated by dermatologists, who tended to prescribe oral antifungals, versus podiatrists, who tended to debride <i>Treatment:</i> patients reported improvement in disease-specific QOL after starting a new treatment, and these improvements continued over 9 months of follow-up	Small sample size, no control group, no mycological confirmation of diagnosis, non-standardization of treatment, recall bias, selection bias	4
Turner [15], 2000	Double-blind RCT (268)	<i>Validated, OM-specific:</i> OM Disease-Specific Questionnaire (ODSQ) with generic core (MOS: general health and well-being scales) and disease-specific questions (symptoms, pain, appearance, physical activities, social activities, stigma, treatment satisfaction) (55)	Generic health questions were less sensitive than disease-specific questions in eliciting QOL differences for clinical change <i>Clinical change:</i> cured and improved patients had higher QOL than the therapeutic failure group, with very large differences for symptom distress and functional impact scores; mycologically eradicated patients also had higher QOL scores than mycologically persistent patients	Poor follow-up with only 268/365 (73%) of enrolled patients analyzed	1
Potter [16], 2006	Open-label, RCT (504)	<i>Validated, OM-specific:</i> OnyCOE-t™ with disease-specific questions (symptoms, appearance problems, physical activities, overall problem, stigma, treatment satisfaction) (33)	Factors worsening QOL: female gender, young age <i>Clinical change:</i> mycological cure resulted in higher scores than uncured patients; an 8.5-point change in OnyCOE-t™ scores correlated with 25% improvement in target nail clearing	Clinical assessments were confined to 1 nail vs. PRO measures disease on all nails, differences were minimal as both groups received treatment	1
Warsaw [17], 2007	Case Series (402)	<i>Validated, OM-specific:</i> NailQoL with dermatology-specific questions (Skindex-29) and disease-specific questions (emotional, social, symptoms) (15)	Generic dermatology questions (Skindex-29) were less sensitive than disease-specific questions in eliciting QOL differences <i>Main concerns:</i> self-consciousness, embarrassment, nail care, concealing nails from others, pain <i>Factors worsening QOL:</i> fingernail involvement, duration of disease, number of nails involved <i>Clinical change:</i> NailQoL scores were improved for complete cure (clinical and mycological) but not for mycological cure only <i>Relative to other diseases (Skindex-29):</i> compared to eczema and body psoriasis, OM QOL was better; compared to NMSC and benign growths, OM symptomatic and functioning impact was similar, but OM emotional impact is worse	No control group, confounding due to terbinafine use, confounding due to comorbidities, lack of generalizability (only veterans included)	4
Tabolli [7], 2007	Cross-sectional study (66)	<i>Validated, dermatology-specific:</i> Skindex-29 (dermatology-specific), General Health Questionnaire (generic), MOS Short Form (generic) (77)	<i>Cultural differences:</i> fingernail disorders impaired QOL less in Italian patients than other countries <i>Relative to other diseases (Skindex-29):</i> compared to other nail disease, OM had worse QOL; compared to dermatitis, warts, erythema, OM had better QOL <i>Relative to other disease (MOS):</i> compared to dermatitis, warts, erythema, OM had better QOL	Use of dermatology PRO may be less sensitive than OM-specific PRO, small sample size, no control group, recall bias, selection bias	4
Szepietowski [13], 2007	Cross-sectional study (3,904)	<i>Validated, OM-specific:</i> questionnaire developed by Drake et al. [12] in Polish (40)	<i>Main concerns:</i> pain, embarrassment, fear of spread to other nails, fear of spread to other people, aesthetic disfigurement <i>Factors worsening QOL:</i> female gender, fingernail, number of nails involved (>5), educational level, towns/cities residence <i>Treatment:</i> patients previously unsuccessfully treated had lower QOL than those who had never undergone therapy	No control group, recall bias, selection bias	4
Szepietowski [25], 2009	Case series (1,684)	<i>Validated, dermatology-specific:</i> stigmatization questionnaire (6)	OM patients had increased feeling of stigmatization <i>Main concerns:</i> others thinking disease is contagious, self-consciousness, self-image <i>Factors worsening QOL:</i> female gender, younger age, fingernail involvement <i>Factors NOT affecting QOL:</i> duration of disease, number of nails involved, educational level <i>Treatment:</i> therapy with combined terbinafine and amorolfine resulted in reduced stigmatization level to 40% of baseline level	No control group, recall bias, selection bias	4

Table 1 (continued)

First author [Ref.], year	Study design (patients, n)	PRO Instrument (questions, n)	PRO outcomes	Limitations	QOE
Milobratovic [14], 2013	Cross-sectional study (140)	<i>Validated, OM-specific:</i> validated generic core from MOS Short Form General Health Survey and toenail-specific scale developed by Drake et al. [12] validated by authors (53)	<i>Main concerns:</i> nail care, bothersomeness, aesthetic disfigurement, footwear limitation, fear of spread to other nails, fear of spread to other people <i>Factors worsening QOL:</i> female gender, duration of disease (2–5 years specifically, no difference >5 years), proportion of individual nails involved ($\geq 70\%$), blue-collar occupation <i>Cultural differences:</i> QOL was worse for Serbian patients than US or Italian patients	Small sample size, no control group, confounding by comorbidities, recall bias, selection bias	4
Bunyaratavej [24], 2015	Cross-sectional study (110)	<i>Validated, dermatology-specific:</i> DLQI (symptoms, daily activities, leisure, personal relationships, treatment) (10)	<i>Factors worsening QOL:</i> female gender, younger age (<60 years) <i>Relative to other disease (DLQI):</i> compared to acne, pigmentary disorders, and psoriasis, OM QOL is better	Use of dermatology PRO may be less sensitive than OM-specific PRO, small sample size, no control group, confounding by different stages of treatment, recall bias, selection bias	4

DLQI, Dermatology Life Quality Index; MOS, Medical Outcomes Study; NR, not reported; OM, onychomycosis; PRO, patient-reported outcomes; QOL, quality of life; RCT, randomized controlled trial; QOE, quality of evidence.

Table 2. Summary of PRO instruments for onychomycosis treatment evaluation

Treatment route, source	Study design	Comparison	PRO instrument	PRO outcomes	Clinical outcomes	Follow-up	Limitations	QOE
Oral, Pollak and Billstein [26]	Case series ($n = 1,534$)	Terbinafine (250 mg daily) for 12, 18, and 24 weeks; no control	NR	More than 80% rated treatment with terbinafine as either “very good” or “good”; 68.8% were very satisfied or satisfied with toenail appearance, 76.0% with treatment results, and 76.3% with the most bothersome aspects of the disease, such as pain with walking or inability to feel one’s toes	Mycological cure rates were 72.1% (12 weeks), 72.5% (18 weeks), and 77% (24 weeks); clinical cure rates were 49.5% (12 weeks), 49.2% (18 weeks), and 44.6% (24 weeks); recurrence rates ranged from 14.1 to 17.3%	72 weeks, number lost to follow-up NR but 110 received insufficient treatment	No control, no randomization, treatment duration contingent on failure to improve at an earlier time point, questionable validation of instrument	4
Oral, Stier et al. [27]	Case series ($n = 147$)	Oral therapy ($n = 58$) vs. non-oral therapy (debridement, topical medications) ($n = 89$)	Questions from Lubeck et al. [18] (nonvalidated, OM-specific), Medical Outcomes Study questionnaire (validated, generic), and Short Form of the Medical Outcomes questionnaire (validated, generic); however, details of actual instrument unclear	Oral therapy group reported statistically significantly improved QOL scores ($p < 0.05$); treatment satisfaction correlated with nail condition; males expressed more satisfaction with treatment than females ($p < 0.01$)	Physician assessment showed greater improvement in the oral therapy group ($p = 0.001$)	9 months, number lost to follow-up NR	No control, no randomization, no standardization of treatment, no mycological confirmation of diagnosis, questionable validity of PRO instrument	4
Oral, Stier et al. [28]	Case series ($n = 124$)	Initial oral therapy ($n = 46$) vs. initial nonoral therapy ($n = 78$)	Toenail Symptom Index: modified from Lubeck et al. [18–19] (validated, OM-specific)	Oral therapy group had greater QOL effectiveness as measured by the Toenail Symptom Index (94 vs. 49%); an additional USD 304–491 was required for each case improved with oral medication over 9 months though extrapolation showed cost equivalence after 17–20 months	Physician global improvement rating showed greater improvement in oral therapy group	9 months, number lost to follow-up NR	No control, no randomization, no standardization of treatment, no mycological confirmation of diagnosis	4

Table 2 (continued)

Treatment route, design, source	Study design	Comparison	PRO instrument	PRO outcomes	Clinical outcomes	Follow-up	Limitations	QOE
Oral, Firooz et al. [29]	Case series (<i>n</i> = 20)	Pulse-dose oral itraconazole (200 mg twice daily for 1 week every 4 weeks for 12 weeks); no control	13 questions from the instrument by Drake et al. [12], the International OM Questionnaire (questionable validity, OM-specific)	After treatment, patients' mean QOL scores were improved (<i>p</i> = 0.009)	16/20 (80%) mycologically cured, 9/20 (45%) clinically cured, 5/20 (25%) improved, 6/20 (30%) did not improve	48 weeks, number lost to follow-up NR (but appears to be 0/20)	Small sample size, no control, questionable validity of PRO instrument	4
Oral, Warsaw et al. [30]	Cross-sectional study (<i>n</i> = 142)	Pulse-dose oral itraconazole (200 mg twice daily for 1 week every 4 weeks for at least 12 weeks) (<i>n</i> = 48) vs. continuous oral terbinafine (250 mg daily for at least 12 weeks) (<i>n</i> = 94)	Morisky Compliance Scale (validated), OnyCOE-t TM Satisfaction Scale (validated, OM-specific), ease and convenience scale (non-validated)	Patients taking terbinafine reported significantly increased ease and convenience (<i>p</i> = 0.008) and significantly greater overall satisfaction (<i>p</i> = 0.003); no difference in compliance	NR (cure rates NR for 2 groups)	N/A	Recall bias, no randomization, not blinded	4
Oral, Potter et al. [31]	Open-label, RCT (<i>n</i> = 504)	Terbinafine (250 mg daily for 12 weeks) and debridement of target toenail (at 0, 6, 12, and 24 weeks) (<i>n</i> = 246) vs. terbinafine only (<i>n</i> = 258)	OnyCOE-t TM (validated, OM-specific)	Terbinafine with adjunct debridement decreases symptom frequency (<i>p</i> = 0.0395), especially thickening/swelling and discoloration, and improves overall treatment satisfaction (<i>p</i> = 0.0077) in patients with toenail OM, though the effect is greatest at the end of the terbinafine course	NR	48 weeks, number lost to follow-up NR	Clinical assessments were confined to 1 nail vs. PRO measures disease on all nails, differences were minimal as both groups received treatment	1
Topical, Malay et al. [32]	RCT (<i>n</i> = 55)	Debridement (every 3 months for 9–12 months) and topical ciclopirox 8% daily (<i>n</i> = 28) vs. debridement only (<i>n</i> = 27)	Bristol Foot Score (validated, podiatry-specific)	Both groups had improved QOL scores (<i>p</i> < 0.001), but adjunct ciclopirox improved QOL more than debridement alone (<i>p</i> = 0.002)	Debridement alone did not result in a single case of mycological cure whereas with the addition of ciclopirox, mycological cure was 76.7%	Median 10.5 months, 2/55 (4%) lost to follow-up	Participants not blinded, lab diagnostics was only performed on one toenail	1
Topical, Tosti and Elewski [33]	Double-blind, RCT (<i>n</i> = 1,655)	Efinaconazole, 10%, daily for 48 weeks (<i>n</i> = 1,236) vs. vehicle (<i>n</i> = 415)	OnyCOE-t TM (validated, OM-specific)	Efinaconazole group had significantly improved mean QOL scores (<i>p</i> ≤ 0.002), significantly higher treatment satisfaction scores (<i>p</i> < 0.001), significantly greater mean change in all domains (<i>p</i> ≤ 0.002); there was a significant correlation between change in percent affected nail and change in mean domain scores	Complete cure rate NR; 47% of patients treated with efinaconazole were considered clinically improved (≤10% nail involvement)	52 weeks, 4/1,655 (0.2%) lost to follow-up	Time period may be too brief, lack of generalizability, clinical assessments performed on one toenail but all nails affect QOL assessment	1
Topical, Snell et al. [34]	Case series (<i>n</i> = 20)	Vicks VapoRub, unclear treatment course; no control	OnyCOE-t TM (validated, OM-specific)	After 24 weeks, fewer patients reported embarrassment (15/20, 75% to 11/18, 61%) and pain or discomfort (11/20, 53% to 7/18, 39%), and 17/18 (94%) of patients reported treatment satisfaction	After 24 weeks, 15/18 (83%) had improvement of affected nails, 2/18 (11%) had complete clearance	48 weeks, 5/20 (20%) lost to follow-up	Small sample size, no control, no blinding, single site, compliance problem, poor follow-up	4
Laser, Ortiz et al. [35]	RCT (<i>n</i> = 10)	1,320-nm Nd:YAG laser, 4 treatments over 24 weeks vs. cryogen spray sham	Nail QOL Questionnaire (unclear if validated as specific questionnaire is not cited, OM-specific)	Patients felt less self-conscious and embarrassed about the treated toe, but there was no significant difference from the control toe	No significant improvement was observed in the treated versus untreated nail	NR	Small sample size, confounding from topical antifungal and sham treatment	2

NR, not reported; OM, onychomycosis; PRO, patient-reported outcomes; QOE, quality of evidence; QOL, quality of life; RCT, randomized controlled trial; Nd:YAG, neodymium:yttrium aluminum garnet.

Table 3. Psychometric properties for evaluating PRO instruments

Psychometric property	Definition	Quantitative evaluation
Variability	Degree to which the full range of item responses and scale scores are reported	
Reliability		
Internal consistency	Reproducibility across items	Cronbach α coefficient >0.70
Test-retest	Reproducibility across time	Intraclass correlation coefficient >0.75
Validity		
Construct	How well a test measures a variable	
Discriminant	Whether constructs without a relationship are unrelated	
Convergent	Whether constructs with a relationship are related	
Responsiveness	Ability to discern meaningful change in disease activity	

in addition to the possibility of an overly sensitive response when no clinical change has occurred.

Drake et al. [12] introduced the International Onychomycosis Questionnaire, which has been evaluated in multiple languages and validated in a Polish cross-sectional study for both toenail and fingernail disease [13]. The toenail-specific scale was also validated in a Serbian cross-sectional study [14].

The fifth validated PRO instrument is the NailQoL, which consists of the previously validated Skindex-29 (a dermatological QOL measure) and 10 questions from nonvalidated disease-specific questionnaires [17]. Subjects with complete cure of the target toenail and all 10 toenails reported significantly improved PRO scores ($p \leq 0.02$).

Finally, Warshaw et al. [30] developed a scale assessing treatment ease and convenience for a cross-sectional study, although a comprehensive onychomycosis instrument was not developed. Warshaw's instrument was valid and responsive with acceptable internal consistency but did not evaluate test-retest reliability.

Treatment

Ten unique studies used PROs to evaluate treatment in onychomycosis patients, none of which included fingernail disease (Table 2). Patient QOL was examined in 6 studies of oral antifungals, 3 studies of topical antifungals, and 1 study of laser therapy. Only 3 studies used a validated, onychomycosis-specific PRO instrument, the OnyCOE-tTM [31, 33, 34]. Four studies used instruments derived from previously validated questionnaires [27–30], 1 study used a validated instrument for podiatry-re-

lated QOL [32], and 2 studies used instruments of unclear origins [26, 35]. There were 2,224 patients in 4 randomized controlled trials, 1,825 patients in 5 case series, and 142 patients in 1 cross-sectional study.

Impact of Oral Therapies on PRO

As systemic antifungals are the standard onychomycosis treatment, most QOL data have been collected from onychomycosis patients treated with oral medications. Potter et al. [31] validated the OnyCOE-tTM in a prospective, randomized, multicenter trial comparing terbinafine alone with the combination of terbinafine and debridement. Both groups experienced QOL improvement. From baseline, debridement significantly improved treatment satisfaction ($p = 0.0077$) and symptom frequency ($p = 0.0395$). Debridement had the most impact in the final week (week 12) of terbinafine treatment; afterwards, the terbinafine-only group had equivocal QOL improvement, suggesting that debridement only had a short-term effect when terbinafine had yet to adequately penetrate the nail plate. While debridement did not cure onychomycosis, it did improve comfort and appearance, thus enhancing QOL.

Multiple studies have used aspects of Lubeck's questionnaire. Stier et al. [27, 28] compared oral antifungals to local therapy in 2 case series. In their cost effectiveness study, QOL was assessed with the Toenail Symptom Index, an instrument using 2 reliable, valid, and responsive scales from Lubeck's questionnaire [10]. Oral medications such as terbinafine, itraconazole, and fluconazole were significantly superior to local treatment such as topical treatments or debridement ($p = 0.003$); patients

Table 4. Content of Five psychometrically evaluated onychomycosis PRO instruments

	Lubeck et al. [18, 19]	International Onychomycosis Questionnaire [12]	ODSQ [15]	OnyCOE-t™ [16]	NailQoL [17]
Items, <i>n</i>	80	40	61	33	15
Content	Generic core + disease-specific (symptoms, appearance, function, stigma, overall problem, treatment satisfaction)	Generic core + disease-specific (social, emotion, and symptoms)	Generic core + disease specific (symptom distress, function, stigma, and overall problem)	Disease-specific only (symptoms, appearance, physical activities, overall problem, stigma, treatment satisfaction)	Disease-specific only (symptoms, function, emotion)
Validation study	Multicenter observational study of 129 patients	Cross-sectional multicenter study of 284 toenail and 248 fingernail patients in France, Italy, Germany, USA	Prospective double-blind, multicenter RCT of 268 patients comparing antifungal vs. placebo	Prospective, multicenter RCT of 504 patients comparing oral terbinafine with adjunct debridement vs. terbinafine alone	Prospective, RCT of 402 patients comparing two terbinafine dosing regimens
Diagnosis	Clinical	Clinical	Mycological	Mycological	Mycological
Location	Toenail	Toenail and fingernail	Toenail and fingernail	Toenail	Toenail
Variability	Poor (ceiling effects)	Good (except for emotional scale)	Good (except for fingernail symptoms scale)	NR	NR
ICR	CAC ≥ 0.76	CAC ≥ 0.60	CAC ≥ 0.79	CAC ≥ 0.84	CAC ≥ 0.88 (except function scale)
TRR	ICC ≥ 0.52	ICC ≥ 0.80	ICC ≥ 0.89 (toe), PCC = 0.79 (finger)	NR	ICC ≥ 0.88
Validity	Construct (physical function with impairment); discriminant (gender, age)	Construct (severity level); discriminant (duration, extent, number of nails affected)	Construct (health status levels, low vs. high impact, treatment outcomes)	Construct (symptom frequency with bothersomeness, embarrassment with stigma, treatment satisfaction with symptom); discriminant (gender, age)	Construct (severity levels)
Responsiveness	40 clinically improved patients vs. 34 stable patients ($p < 0.05$ for all disease-specific scales except stigma)	NR	28 clinically cured vs. 168 clinically improved vs. 45 failed patients (QOL change and clinical improvement correlation)	400 clinically improved vs. 37 stable patients (Guyatt statistic indicates moderate to high responsiveness; $p < 0.02$ on all scores except symptom bothersomeness)	61 complete cure of all toenails vs. 231 without ($p \leq 0.01$); 100 complete cure of target toenail vs. 191 without ($p \leq 0.02$)

NR, not reported; RCT, randomized controlled trial; ICR, internal consistency reliability; CAC, Cronbach α coefficient; TRR, test-retest reliability; ICC, intraclass correlation coefficient; PCC, Pearson correlation coefficient. Number of items refers to the number of questions included in the tool. Content examines whether the questionnaire included a generic core asking general health questions and what specific categories were included amongst the disease-specific questions. Validation study describes the study design used to validate the tool. Diagnosis states how onychomycosis was diagnosed in the enrolled participants of the validation study. Location indicates whether the tool was validated in toes, fingers, or both. Psychometric validation variables variability, ICR, TRR, validity, and responsiveness are as described in Table 3.

treated with oral medications also had greater direct medical expenses with an additional cost of USD 304–491 for each case improved over 9 months, although extrapolation showed eventual cost equivalence [28]. The patient satisfaction study by Stier et al. [27] demonstrated that treatment satisfaction was correlated with nail condition, although the content of the questionnaire was unclear. Warshaw et al. [30] used the treatment satisfaction scale from Lubeck's questionnaire in their study of terbinafine versus pulsed-dose itraconazole in a multicenter, cross-sectional study with 142 patients. Subjects reported greater ease and satisfaction with terbinafine ($p = 0.008$ and $p = 0.003$, respectively).

Using an instrument modified from Drake's international questionnaire, Firooz et al. [29] evaluated the impact of itraconazole pulse therapy on the QOL of 20 toenail onychomycosis patients and reported that mean QOL scores significantly improved with treatment. However, with this incomplete instrument modified from Drake's validated tool, no rationale was provided regarding the items chosen for the questionnaire; thus, the reliability and validity of this instrument are in question.

Finally, the earliest use of QOL metrics in onychomycosis treatment was Pollak and Billstein's evaluation of terbinafine efficacy using a large, multicenter, open-label study of 1,534 toenail onychomycosis patients [26]. Patients reported overall satisfaction with the treatment results and improved symptom severity. The details of the PRO instrument were not included.

Impact of Topical Therapies on PRO

PRO analyses of topical treatments are limited, likely in part because numerous studies have demonstrated the clinical superiority of oral medications [36, 37]. Additionally, until recently, ciclopirox was the only topical drug approved for onychomycosis treatment in the US [36]. With the approval of efinaconazole and tavaborole in 2014, more QOL studies are warranted given the high cost and nonsuperiority of these medications to oral antifungals [37].

Tosti and Elewski [33] used the OnyCOE-tTM to evaluate the impact of topical efinaconazole versus vehicle on PROs in a 48-week, randomized, multicenter, double-blind study with 1,655 toenail onychomycosis patients. The efinaconazole group had significantly greater mean QOL scores across all domains ($p \leq 0.002$) and significantly higher treatment satisfaction scores ($p < 0.001$). The improvement was especially marked for the 47% of subjects who were considered clinically improved. Notably, even subjects in the efinaconazole group who failed to demonstrate clinical

improvement had better scores for symptom frequency, appearance, and overall problem as compared to baseline, suggesting that even the smallest change in nail appearance can improve QOL. The change in percent nail affected correlated with change in mean domain scores.

Patients with HIV are at higher risk for onychomycosis and yet are an understudied group. The OnyCOE-tTM was also used in a 48-week prospective study of Vicks VapoRub for treating toenail onychomycosis in 20 HIV-positive subjects [34]. This treatment is a non-FDA-approved modality containing eucalyptus oil, a natural home remedy for onychomycosis with little-to-no evidence of clinical utility. After 24 weeks of treatment, fewer patients reported embarrassment and pain/discomfort, and 94% of patients reported treatment satisfaction. Limitations of this study included small sample size, poor follow-up, and poor adherence. Additionally, PRO data were not analyzed for statistical significance.

Malay et al. [32] used the Bristol Foot Score, a validated, podiatry-specific PRO instrument to evaluate QOL in 55 toenail onychomycosis patients who underwent either debridement alone or debridement with adjunct ciclopirox treatment in a multicenter randomized controlled trial. Debridement alone did not result in any mycological cure, while the addition of ciclopirox resulted in a cure rate of 76.7%. Both groups had improved QOL scores ($p < 0.001$), but the addition of a topical lacquer improved QOL more than debridement alone ($p = 0.002$).

Impact of Laser Therapy on PRO

Given that achieving cure for onychomycosis requires prolonged treatment, investigations have turned towards alternative modalities to improve clinical response. Laser, light, and combination therapy provide modalities that free patients from the burden on daily medication adherence and drug-drug interactions [38]. Although there have been hundreds of recent studies examining lasers to treat onychomycosis, PRO analyses are limited. Ortiz et al. [35] investigated the efficacy of the 1,320-nm neodymium:yttrium aluminum garnet laser in a 24-week, randomized, placebo-controlled study of 10 subjects with bilateral great toe onychomycosis. Overall, no significant improvement was observed in treated versus untreated nails. A questionnaire was used to evaluate PRO, although its contents were not identified. Patients reported less self-consciousness and embarrassment about treated toenails despite no clinical difference. Limitations of this study included small sample size, concomitant treatment with a topical antifungal, and possible therapeutic effect of the sham treatment.

Discussion

Although onychomycosis has traditionally been viewed as a cosmetic problem, PRO analyses have demonstrated the substantial morbidity of this disease [5, 7, 10, 18–22]. This review identified 5 psychometrically evaluated instruments that can evaluate patient QOL: Lubeck's [10] and Drake's [12] instruments as well as the ODSQ [15], OnyCOE-t™ [16], and NailQoL [17]. Only the OnyCOE-t™ has been used in its entirety [31, 33, 34]. In practice, patient responses in these QOL instruments have paralleled clinical change, which lends to their credibility. Additionally, PRO instruments allow practitioners to codify and translate subjective patient experiences into quantitative data.

While onychomycosis is not life-threatening, in studies of the effect of onychomycosis on QOL, 92% of patients reported negative psychosocial or physical impairments [22], and 70% of patients considered onychomycosis to be at least a moderate problem [23]. Compared to controls, onychomycosis patients had significantly poorer QOL in general health perception, bodily pain, mental health, social functioning, health concern [18, 19], physical appearance [13, 14, 17–19, 25], and physical functioning, such as limitations with standing and working with one's fingers [12, 14, 18–21, 23]. Onychomycosis patients were more self-conscious [17–19, 22, 25] and embarrassed [12, 13, 17–19, 21, 23], feared spread of transmission to other nails or other people [12–14, 22, 25], and experienced pain [12, 13, 17–23]. In using the validated, dermatology-specific instrument Skindex-29, onychomycosis QOL impairment was worse than other nail disorders [7], comparable to nonmelanoma skin cancer and benign growths [17], and better than eczema and body psoriasis [17]. This morbidity is not always readily evident. Pain associated with onychomycosis is often underestimated by physicians [12], and although clinicians may not appreciate any clinical change after treatment, patients report improved QOL [33].

To assess patient QOL, 5 PRO instruments have been validated for onychomycosis. Drake's questionnaire is the only instrument validated in multiple languages but also the only one without data on responsiveness, thus limiting its use in monitoring disease activity. Drake's questionnaire and the ODSQ are the only instruments validated for fingernail disease, although the ODSQ does not explicitly list fingernail-specific items. The validation studies for the ODSQ, OnyCOE-t™, and NailQoL established diagnosis by mycological criteria; the validity of Lubeck's and Drake's instruments may be questionable as

patients could have had nonfungal nail disease. Though earlier validated questionnaires included general health measures, the OnyCOE-t™ and NailQoL assess only onychomycosis-specific items. A generic core allows comparisons across interventions and diseases as it uses previously validated measures to evaluate parameters of general health distress, psychosocial well-being, and physical functioning [7, 17, 24]. However, this core also has low sensitivity to group differences and clinical changes [10, 12, 15, 17–19]. It also lengthens questionnaires, making clinical implementation less feasible [9], which may explain why Lubeck's and Drake's questionnaires have not been utilized in their entirety though selections from each have been appropriated [27–30]. To date, only the OnyCOE-t™ has been used in full [31, 33, 34]. The OnyCOE-t™'s popularity may be secondary to its shorter length and defined MCID, which allows clinicians to correlate PRO data with clinical change.

The majority of PRO data for treatment assessment parallel clinical data: oral antifungals have higher cure rates and also larger QOL changes when compared to topicals [26–28]; terbinafine is superior for clinical improvement and treatment satisfaction when compared to pulsed-dose itraconazole [30]. However, with new topical antifungal medications and increasing interest in laser and light therapy, PROs are important to understand patient priorities. In a 1998 study, although 79% of patients asked about treatment for onychomycosis, 26% reported that their providers discouraged medication use [19]. Even if insurance would not cover the cost, 97% of patients were willing to pay for medications with an 80% cure rate; 57% were still willing to pay even if the cure rate dropped to 35% [23]. This is particularly relevant given the recent introduction of expensive topical therapies for onychomycosis. Efinaconazole has been reported to result in improvement in only 42.6% of patients, and yet has been reported to improve QOL domains even in patients without appreciable clinical improvement, which further emphasizes that patient QOL cannot be deduced from clinical exam alone [33]. PRO instruments are essential for optimizing treatment to maximize compliance, treatment satisfaction, and QOL.

It should be noted that some studies are limited by their study design. For example, Ortiz et al. [35] showed that patients undergoing laser treatment had QOL improvement without significant clinical change, suggesting that laser therapy can be worthwhile for onychomycosis patients; however, the validity of the conclusion is limited by a small sample size and concurrent antifungal use. Additionally, the effect of disease recurrence on pa-

tient QOL and willingness to pay was not evaluated. Given such limitations, study results should be extrapolated with caution, particularly when patients may face exorbitant expenses for a therapy that may not be clinically effective or offer long-term, sustained results.

It is worth noting that the reviewed literature does not address the differences between subjects presenting with a specific complaint of onychomycosis versus those in which the disease is an incidental, and sometimes unconvincing, finding. Research subjects and patients seeing a specialist for onychomycosis are self-selecting and may disproportionately reflect QOL impairment. Given that, it is difficult to quantify the extent of QOL impairment, or perhaps even to firmly establish that onychomycosis is the cause of QOL impairment without comparison to a non-self-selecting control group with incidental onychomycosis. It is possible that QOL impairment may not be a reflection of onychomycosis per se, but more a marker of a threshold of QOL impairment necessary for patients to present to a dermatologist.

Future research should include psychometric evaluation of these instruments in special populations, fingernail disease, and between patients self-selecting for onychomycosis and controls with onychomycosis as incidental findings. For example, HIV and diabetes mellitus are risk factors for onychomycosis and may modify disease type and course, but most PRO trials exclude patients

with these comorbidities. Additionally, neither the OnyCOE- τ^{TM} nor the NailQoL instrument is validated for fingernail disease despite the fact that fingernail involvement has been shown to increase patient disease burden [17, 23].

Conclusion

As medical practice increasingly emphasizes patient-centered care and shared decision-making, QOL assessments are becoming increasingly important. Through PRO instruments, it is apparent that onychomycosis is not only a cosmetic hindrance but also a burdensome medical disorder that patients want and are willing to treat, at times even for limited or no clinically apparent benefit. Five PRO questionnaires have been validated for onychomycosis, and they have been infrequently used in clinical studies examining treatment efficacy. Future research should utilize these instruments to generate further insight into patients' assessment of their health status and of new therapies.

Disclosure Statement

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