

The Impact of Onychomycosis on Quality of Life: A Systematic Review of the Available Literature

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Keywords

Quality of life · Onychomycosis

Abstract

Purpose: Onychomycosis is a nail disorder that is increasing in prevalence worldwide. The psychological and social limitations caused by onychomycosis can potentially undermine the work and social lives of those experiencing these negative effects. This review aimed to evaluate the randomized controlled trials (RCTs) available in the current literature on the impact onychomycosis has on quality of life (QoL).

Methods: A systematic review was performed using the databases PubMed, PsycINFO, Scopus, ClinicalTrials.gov, and Cochrane Library on July 18, 2017. Only RCTs with clinical effects described in English were included for review. **Results:** Ten RCTs reported QoL outcomes for patients suffering from onychomycosis. Treatment satisfaction was statistically significant from baseline to end of treatment in 100.0% (4/4) measures which reported on satisfaction with treatment; mental health was also significant in 100.0% (3/3), symptoms index rating in 100.0% (2/2), symptom frequency in 75.0% (3/4), overall problems in 75.0% (3/4), functional activities in 75.0% (6/8), appearance problems in 66.7% (2/3), symp-

tom distress in 57.1% (4/7), and stigma in 40.0% (2/5). The OnyCOE-t™ and the NailQoL were the most used common outcome measures to describe QoL. **Conclusion:** The study sanctions that onychomycosis physically and psychologically distresses patients' lives. Further research should include validated outcome measures to more effectively treat onychomycosis.

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Introduction

Finger- and toenails not only serve as protection for the surrounding soft tissue having sensory and mechanical functions, they also function as a visual advertisement of a person's overall health. Onychomycosis, or tinea unguium, is a fungal infection of the nail caused by dermatophytes, yeast, and mold. It is the most common nail disorder experienced worldwide; roughly 50–60% of all nail dystrophies are onychomycosis [1]. It more frequently affects the toenails than the fingernails and is characterized by nail thickening, splitting, roughening, and discoloration. The prevalence of the disease increases with a variety of risk factors such as older age, abnormal nail

morphology, immunodeficiency, and genetic factors [2–5]. Due to its high prevalence, onychomycosis constitutes a substantial health issue as it can have certain negative health consequences such as pain, discomfort, and physical impairment. Moreover, the psychological and social limitations caused by onychomycosis can potentially undermine work and social lives. Reviews on this matter reveal a psychological and psychosocial impact as high as 92% [6]. Some studies have found that onychomycosis has an impact on quality of life (QoL) comparable to that of nonmelanoma skin cancer and benign growths [7]. Still, some physicians choose to not always treat onychomycosis, as they view the condition as a cosmetic concern rather than one of actual medical significance. Most patient concerns stem from the unsightly condition of the nail, thus the impact on patients' QoL can be undervalued and overlooked. This review aimed to evaluate the randomized controlled trials (RCTs) available in the current literature on the impact onychomycosis has on QoL.

Methods

A literature search was done on July 18, 2017 for RCTs reporting QoL in onychomycosis. No date ranges were set. Multiple research databases including Scopus, PubMed, PsycINFO, ClinicalTrials.gov, and Cochrane Library were examined; the search terms were a combination of “onychomycosis” and “quality of life” for all searches. Additional limits included removing duplicates and limiting items to English language and humans. The references of retrieved articles were also searched to identify additional articles that might have been missed in the primary database search. Articles that studied nail, foot, or hand pathology in general and did not separate onychomycosis from other pathologies were excluded from review. Both finger- and toenails were included for this review. When studies reported cure rates, mycological cure was defined as any negative culture or negative PAS, clinical cure was defined as 100% normal nail or clinically normal or clear target nail, and complete cure was defined as both mycological and clinical cure. Papers which met explicit inclusion criteria were included for full-text review.

Results

Study Characteristics

Our literature search of multiple databases yielded 312 studies (Fig. 1). Ten RCTs met our inclusion criteria and were included for review [7–16] (Table 1). Articles publication dates ranged from June 1998 [12] to February 2017 [14]. The United States was the origin of publication for all articles [7–13, 15, 16], with the exception of one article published in Spain [14]. Six RCTs reported QoL

data in combination with oral antifungal treatment (4 treated with terbinafine [7, 10, 11], 1 with fluconazole [12], and 1 with various unreported oral antifungal drugs [8]) in 1,998 participants aged 12–87 years. Four RCTs reported topical treatments (two reported ciclopirox [9, 15], one reported efinaconazole [16], and one reported methylaminolevulinic acid-based photodynamic therapy [14]) in 1,790 participants aged 2–98 years. One RCT reported devices for treatment (1,320-nm Nd:YAG laser [13]) in 10 participants aged >18 years. Six different QoL outcome measures were used to measure general QoL in participants; a general, investigator-generated QoL questionnaire [12, 15], the Onychomycosis-Related QoL Questionnaire (Onycho-QoL Questionnaire) [14], the NailQoL [7, 13], the OnyCOE-t™ [10, 11, 16], the Bristol Foot Score (BFS) [9], and the Onychomycosis Disease-Specific Questionnaire (ODSQ) [8].

OnyCOE-t™

Three studies used the OnyCOE-t™ as their main QoL outcome measure after treatment with antifungals (efinaconazole and terbinafine) [10, 11, 16]. Clinical cure was reported as a combined rate of 88.5% (400/452) [11]. Tosti and Elewski [16] found that the treatment group provided statistically significant improvement in all aspects of the OnyCOE-t™ compared to the vehicle treatment. Potter et al. [11] showed significance in two-sample *t* tests between the treatment and the placebo group on all items ($p < 0.0001$ to $p = 0.0176$) except for the symptom bothersomeness ($p = 0.3384$). Later, Potter et al. [10] found that only symptom frequency and treatment satisfaction significantly improved in the treatment group compared to the placebo group ($p = 0.0395$ and $p = 0.0077$, respectively) (Table 2).

NailQoL

Two studies reported the NailQoL as their main outcome measure; one used Nd:YAG laser [13] as treatment and the other used terbinafine [7]. Average mycological cure was 60.5% for the treatment group and 64.5% for the control group [7, 13]. Clinical cure was 45.0% for the treatment group and 29.0% for the control [7]. Complete cure was 40.0% for the treatment group and 28.0% for the control group [7]. Warshaw et al. [7] found that NailQoL scores from baseline to 18 months decreased on average by at least 13 points in the patients with complete cure of the target toenail versus those without, and by at least 16 points in the patients with complete cure of all ten toenails versus those without ($p < 0.01$ and $p < 0.01$). These observed reductions are statistically significant, and for

Table 1. Study characteristics of therapies for the treatment of onychomycosis

Reference (first author)	Treatment	Age, years (mean ± SD)	Sex (M/F)	Presentation	Culture
<i>Oral antifungals (n = 1,952)</i>					
Ling [12], 1998 (n = 384)	fluconazole	treatment: 49.9±14.1;	1,081/487	DSO (n = 652)	<i>Trichophyton rubrum</i> (n = 375), <i>Trichophyton mentagrophytes</i> (n = 7), <i>Trichophyton tonsurans</i> (n = 2)
Turner [8], 2000 (n = 268)	various	control: 48.7±12.9			
Potter [11], 2006 (n = 504)	terbinafine				
Potter [10], 2007 (n = 504)	terbinafine				
Warsaw [7], 2007 (n = 292)	terbinafine				
<i>Topical antifungals (n = 1,790)</i>					
Friedlander [15], 2013 (n = 40)	ciclopirox	treatment: 33.1±9.7;	69/47	DSO (n = 335),	<i>Aspergillus</i> spp. (n = 32), <i>Aspergillus sydowii</i> (n = 2), <i>Aspergillus terreus</i> (n = 2), <i>Candida</i> spp. (n = 71), <i>Candida albicans</i> (n = 10), <i>Epidermophyton floccosum</i> (n = 6), <i>Fusarium</i> spp. (n = 3), <i>Scopulariopsis brevicaulis</i> (n = 2), <i>Trichophyton mentagrophytes</i> (n = 25), <i>Trichophyton rubrum</i> (n = 96)
Malay [9], 2009 (n = 55)	ciclopirox	control: 34.9±9.9		WSO (n = 13),	
Tosti [16], 2014 (n = 1,655)	efinaconazole			TDO (n = 11),	
Gilaberte [14], 2017 (n = 40)	MAL			SHO (n = 9),	
				endonyx (n = 8), PSO (n = 5)	
<i>Devices (n = 10)</i>					
Ortiz et al. [13], 2014 (n = 10)	Nd:YAG laser	>18	-	-	-

DSO, distal subungual onychomycosis; MAL, methylaminolevulinate; PSO, proximal subungual onychomycosis; SD, standard deviation; SHO, subungual hyperkeratosis onychomycosis; TDO, total dystrophic onychomycosis; WSO, white superficial onychomycosis.

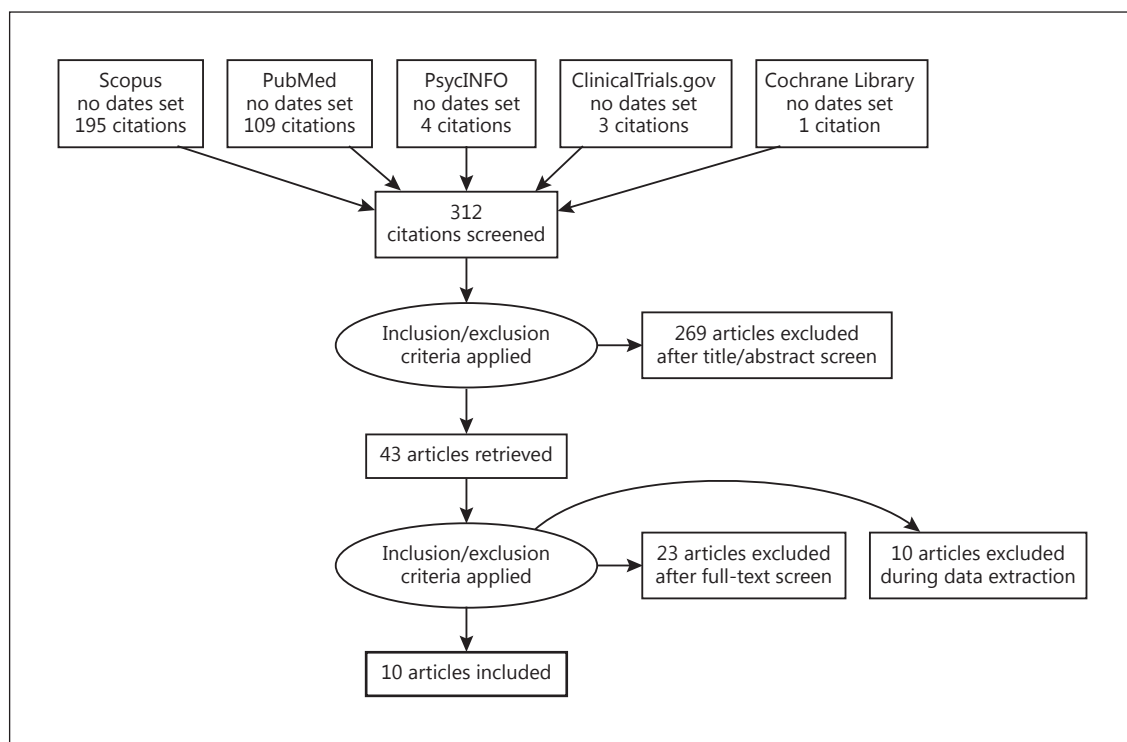


Fig. 1. Study selection process.

Table 2 (continued)

Reference (first author)	Treatment vs. control	Measured, weeks	Clinical results		QoL results post treatment			Adverse events					
			mycological cure ^a	complete cure ^a	clinical cure ^a	symptom frequency	symptom bothersomeness	physical activities problems	appearance problems	overall problems	stigma	treatment satisfaction	
Onychomycosis-Related QoL Questionnaire (n = 40)													
Gilaberte [14], 2017 (n = 40)	3 weekly MAL-PDT sessions vs. 3 weekly placebo PDT sessions	8.3	T: 31.8% (7/22) C: 11.1% (2/18)	T: 18.2% (4/22) C: 5.6% (1/18)	-	PDT vs. MAL-PDT: <i>p</i> = 0.604							Mild to moderate events: pain, pigmentation, inflammation, tinea pedis (n = 1); discontinued
ODSQ (n = 259)													
Turner [8], 2000 (n = 259)	4-m daily treatment and 5-m placebo group vs. 6-m treatment and 3-m placebo group vs. 9-m treatment group vs. 9-m placebo group	9.0	38.8% (100/258)***	-	11.6% (30/259)***	ODSQ (clinical response) Symptom distress: pain <i>p</i> = 0.107, appearance <i>p</i> < 0.001 ^b Functional impact: activities <i>p</i> = 0.127, appearance <i>p</i> < 0.001 ^b , care <i>p</i> = 0.007 ^b Social stigma: acceptance <i>p</i> = 0.222, desirability <i>p</i> = 0.236, overall problems <i>p</i> = 0.034 ^b							-
<p><i>ODSQ chance scores using MOS-SF36</i></p> <p>Mental health: <i>p</i> < 0.01^b toe symptoms-pain, foot-related activities, social acceptance, overall protocol; <i>p</i> < 0.001^b toe symptoms-appearance, nail appearance</p> <p>Health distress: <i>p</i> < 0.01^b toe symptoms-appearance; nail appearance, overall problems; <i>p</i> < 0.001^b foot care</p> <p>Physical functioning: <i>p</i> < 0.001^b foot care</p>													

BFS, Bristol Foot Score; C, control; d, day; D+I, ANL, debridement and topical ciclopirox 8% daily; DO, debridement only daily; m, month(s); MAL-PDT, methylaminolevulinate-based photodynamic therapy; MOS-SF36, 36-item Medical Outcome Survey-Short Form; ODSQ, Onychomycosis Disease-Specific Questionnaire; PDT, photodynamic therapy; QoL, quality of life; T, treatment. ^a Mycological cure: negative cultures or negative PAS; clinical cure: 100% normal nail or clinically normal or clear target nail; complete cure: both mycological and clinical cure. ^b Statistically significant. ^c Children. ***MANOVA.

both outcomes are roughly twice the reduction reported by patients who did not achieve cure status. NailQoL component and total scores of patients achieving mycological cure of the target toenail were not statistically significantly different for patients who did not achieve mycological cure of the target toenail. Similarly, the average change in NailQoL scores for patients with versus without mycological cure of the target toenail alone was not significantly different for any of the component scores or the total NailQoL score. Ortiz et al. [13] found that patients felt less self-conscious and embarrassed about the treated toe versus the untreated toe; however, no significant difference was found for the placebo toe (Table 2).

QoL Questionnaire

Two studies used general QoL questionnaires after treatment with fluconazole [12] or ciclopirox [15]. The weighted average of mycological cure was 52.1% (137/263) for the treatment group and 9.8% (8/82) for the control group [12, 15]. Complete cure was 25.0% (57/228) for the treatment group and 1.2% (1/81) for the control group [12, 17]. Friedlander et al. [15] asked participants after treatment with ciclopirox whether they would undergo this treatment again, with >90% of participants answering yes, indicating an increased QoL effect post treatment. Ling et al. [12] used a questionnaire that addressed general health domains such as mental health and physical functioning as well as disease-specific domains. They found that the treatment groups had significantly better toenail symptoms index scores (*p* < 0.001) compared to the placebo group; furthermore, at the 6 month follow-up visit, the 9-month fluconazole treatment group also had a significantly higher rating than the 4-month treatment group (*p* < 0.05). At every assessment after baseline, all fluconazole treatment groups reported significantly greater satisfaction with treatment (*p* < 0.005), once again indicating an increased QoL effect post treatment.

Various Treatments

Three studies used other various QoL outcome measures: the BFS [9], the ODSQ with the 36-item Medical Outcome Survey-Short Form [8], and the Onycho-QoL Questionnaire [14]. Mycological cure for the BFS was reported per nail sample in 76.7% (99/129 nails) for the treatment group and in 0.0% (0/160 nails) for the control group [9], the Onycho-QoL Questionnaire reported 31.8% for the treatment group and 11.1% for the control group [14], and the ODSQ reported 38.8% combined my-

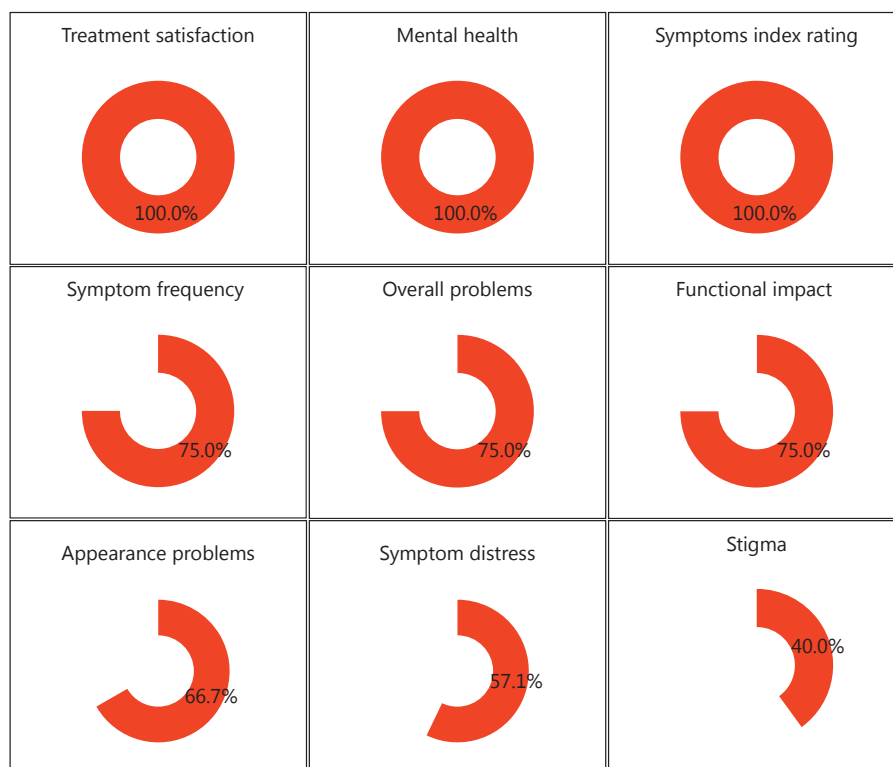


Fig. 2. Frequency of combined statistically significant quality of life outcomes.

cological cure [8]. Clinical cure was reported as a combined cure rate in 11.6% (30/259) [8], and complete cure was 18.2% (4/22) for the treatment group and 5.6% (1/18) for the control group [14]. Turner and Testa [8] reported the ODSQ; the responsiveness change in clinical response showed that patients had an improved QoL effect in the symptom distress group; appearance ($p < 0.001$), functional impact appearance and care ($p < 0.001$ and $p = 0.007$, respectively), and overall problems ($p = 0.034$) post treatment. Gilaberte et al. [14] reported the Onycho-QoL Questionnaire, which showed a p value of 0.604 for the difference between the treatment and the placebo group.

Combined QoL Outcomes and Adverse Events

Treatment satisfaction was reported as statistically significant from the first measurement at baseline and when it was measured again at the end of treatment in 100.0% (4/4) of the measures which used it, mental health was significant in 100.0% (3/3), symptoms index rating in 100.0% (2/2), symptom frequency in 75.0% (3/4), overall problems in 75.0% (3/4), functional activities in 75.0% (6/8), appearance problems in 66.7% (2/3), symptom distress in 57.1% (4/7), and stigma in 40.0% (2/5) (Fig. 2). Four studies reported adverse events from terbinafine, ciclopirox, methylaminolevulinic acid-based photodynamic

therapy, and various oral treatments [7, 12, 14, 15]. A total of 406 participants experienced mild to moderate adverse events thought to be related to treatment with a frequency of 10.5% (406/3,850); 0.6% (22/3,850) of participants discontinued use of the drug due to these effects. Reasons for discontinued use of treatment included gastrointestinal issues, erythema, rash, dizziness, headache, asymptomatic chemical hepatitis, anxiety, oral ulcers, pleurisy, impotence, elevated liver function tests, pain, pigmentation, inflammation, and tinea pedis.

Discussion

QoL refers to outcome measures, management, and an individual's functional level and acuties of well-being that have been affected by a specific disorder. Research done on QoL applies directly to the clinical setting as it offers insight into disease-specific measures that are responsive to therapeutic change. Physical function and positive mental health are influenced by variables that describe physical symptoms, role fulfillment, as well as psychological and social parameters [18]. In this review, we found ten RCTs that reported QoL outcomes among patients suffering from onychomycosis [7–16]. The

OnyCOE-tTM was the most commonly reported measure, with the NailQoL and Drake's QoL Questionnaire as the next frequently reported measures. Mental health, treatment satisfaction, and symptom index were the most consistently statistically significant reported outcomes; however, all extractable measures showed significant improvement. Social stigma of onychomycosis was the only measure with less improvement over time, with 40% of reported outcomes showing significance. Our results demonstrate that most measurable QoL outcome measures reported a statistically significant difference in the treatment satisfaction scores between those patients who showed clinical improvement and those who did not. Thus, onychomycosis has the potential to create serious problems that may significantly affect QoL and well-being [19, 20]. These reported symptoms of onychomycosis have the impendence to be seriously distressing and can lead to an impact on functionality and mental health.

Most activities of daily living encompass some form of manual dexterity or walking and standing. These activities, as well as work and social activities, may be compromised with a positive diagnosis of onychomycosis. Even simple measures such as wearing shoes and appropriately manicuring nails may prove challenging [21]. Fortunately, onychomycosis was not reported as having a significant negative effect on sex life; however, duration of disease as well as fingernails and number of nails involved have been seen to be significant predictors of QoL scores [7, 18, 22–24]. Another concern is that the presence of a deteriorating mycotic nails may produce adjacent skin injury, thus creating exposure to other organisms and increasing the risk of infection [25, 26]. Psychosocially, the nail represents an important component of communication [19]. Modern society values cosmetic appearance and Canada alone in 2017 has a nail industry worth CAD 5 billion, which is growing annually by 2.4% and employs 68,678 people in 24,868 businesses [27]. Attractive, healthy, well-maintained nails signify physical well-being, youth, and cleanliness; consequently, mycotic infections can create issues of self-confidence.

The physical symptoms of onychomycosis are indeed bothersome; however, the psychological implications are even more harrowing [28, 29]. Multiple studies report the presence of anxiety and depression associated with onychomycosis along with low body image and self-esteem, which in turn deteriorates one's sense of worth [30–33]. Affected persons may additionally be less willing to participate in social and leisure activities, furthering the already deteriorated mental state [34]. Patients with psoriasis, atopic dermatitis, or other skin diseases frequently

report experiencing stigmatization due to the presence of their condition [33, 35, 36]. Fingernail versus toenail onychomycosis has been reported to be responsible for a markedly greater psychological impact [33]. This is most likely due to the fact that fingernails are more visible to other people and toenails can be hidden with shoes or socks. Comparison between women and men revealed that only some aspects of social isolation were experienced to a greater extent by the female than the male patients [33].

In addition to the physical and mental implications of onychomycosis, the economic burden is congruently an important QoL discussion. In 1994, Scher [28] reported that 662,000 Medicare patients made 1.3 million visits to physicians in 1989–1990, costing the United States health-care system USD 43 million. Workplaces also suffer, as one multicenter telephone survey of patients with onychomycosis found that there was an average of 1.8 onychomycosis-related sick days per 258 participants [37]. For individuals who are experiencing financial hardship, an onychomycosis diagnosis can be worrying. Furthermore, onychomycosis may exacerbate financial stress, thereby influencing their livelihood as well as their ability to maintain employment benefits, including health insurance, and potentially manage other financial obligations.

Individuals suffering from concomitant conditions are at a particularly high risk, and a strong clinical incentive is necessary in order to prevent primary disease-related complications [21]. Special patient populations such as the elderly or children are at further risk of physical deterioration, and functional limitations create unique challenges for daily life [21]. The inability to perform basic self-care acts can be quite significant in, for instance, diabetics, where fungal nail infections are known to contribute to the severity of diabetic foot problems. Diabetes mellitus in the elderly is very concerning, and if allowed to evolve unimpeded, progressive disability, cellulitis, osteomyelitis, and tissue necrosis may transpire with the ramification of major lower limb amputation [38]. Even the psychosocial implications of onychomycosis may be intensified in special populations, as the visible reminder of current negative health status and immune system deterioration often has a profound emotional impact [39].

Five QoL measures have been validated for use in patients with onychomycosis; however, very few are used in high-quality clinical trials. The current validated measures for onychomycosis and QoL are the NailQoL, the OnyCOE-tTM, the ODSQ, the Onycho-QoL Questionnaire, and the International Onychomycosis Questionnaire. The first reference of a validated instrument for

measuring QoL in onychomycosis, called the Onychomycosis QoL Questionnaire, was produced by Lubeck et al. [23]; the revised version of this instrument has been validated and is in use today [24]. Turner and Testa [8] are responsible for the ODSQ, which can be used in both toe- and fingernails and derives questions from the Lubeck measure. The OnyCOE-t™ is also derived from the Lubeck instrument [11]. The Onycho-QoL Questionnaire is also able to be used in both finger- and toenails and is available in multiple languages [40, 41]. The NailQoL is a combination of the Skindex-29 and 10 additional questions [7].

Clearly, other nail disorders such as trauma, alternative infections, structural abnormalities, psoriasis, paronychia, and other inflammatory diseases cause similar frustration to patients. However, the impact of onychomycosis on QoL compared to other nail disorders was statistically significantly higher; specifically, QoL was more affected in patients having multiple nails involved, in women, and in people aged 60–79 years [42]. Yet, there was no statistically significant difference in the QoL impact between patients having only fingernails or only toenails involved, indicating that the option to hide toenails does not necessarily act to decrease psychosocial impairment [42]. In conclusion, onychomycosis can have substantial negative consequences on QoL. Effective antimy-

cotic therapy might not only improve the physical symptoms of onychomycosis, but also the patient's mental health and social functioning as well as QoL. Onychomycosis needs to be seen as an important problem for a patient which significantly reduces their physical and mental well-being. Individuals' mental perception of the appearance of their nails is an important dermatologic construct as body image dissatisfaction can have a profound impact upon their QoL [43]. Disease-specific instruments have been shown to be better at defining major problems in patients with more accuracy [7, 11, 22, 40]. The continued use of health-related QoL measurements in clinical research allows a more accurate description of how nail disorders affect patients and shows the relevance of some neglected aspects such as pain or emotional trauma [44]. Proper and homogenous assessment of QoL offers us the opportunity to address issues in a more patient-centered approach to treatment.

Disclosure Statement

A.K. Gupta is a clinical trials investigator and speaker for Valeant Canada, a clinical trials investigator for Moberg, and a consultant for Sandoz. R.R. Mays is employed by Mediprobe Research Inc., a site where clinical trials are run under the supervision of A.K. Gupta.

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