



On the Basis of Sex: Impact and Treatment of Toenail Onychomycosis in Female Patients

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Onychomycosis is a fungal infection of the nail unit affecting approximately five percent of the global population and representing 50 percent of all nail dystrophies seen in clinical practice. Patients with onychomycosis can suffer significant pain in addition to physical and psychological distress, which may seriously impair their quality of life (QoL). It is well established that onychomycosis prevalence is impacted by patient characteristics, including age and systemic comorbidities. However, the impact of patient sex on onychomycosis occurrence and treatment is not well characterized. This narrative review of the literature was conducted to address a dearth of published information on epidemiology, QoL, clinical trial participation, and treatment success specifically in female patients with onychomycosis. Additionally, an analysis of real-world treatment of onychomycosis in female patients is reported, including prescription patterns and the impact of toenail polish on topical treatments for onychomycosis. Understanding sex as a clinically relevant variable may inform onychomycosis treatment strategies and improve treatment outcomes.

KEYWORDS: Fungal infection, toenail, nail disorders, onychomycosis, gender, women, efinaconazole, topical

Onychomycosis is a fungal infection of the toenails or fingernails caused by dermatophytes, nondermatophyte molds, or yeasts.¹ Treatment duration of onychomycosis can be long, as achieving complete cure—comprising a normal appearing nail plate, negative nail fungal culture, and negative potassium hydroxide—may take 12 months or more in toenails due to slow nail growth.² Additionally, the relapse/reinfection rate is at least 20 to 25 percent.³

Patient factors can impact onychomycosis occurrence and are important to consider when evaluating treatment options with antifungals.⁴ For example, increasing age is a well-accepted risk factor for onychomycosis,⁵ as are systemic comorbidities such as diabetes.⁶ Since 2001, NIH-defined Phase III clinical trials must include valid subgroup analysis by sex/gender if a difference in outcome is expected among groups.⁷ However, published analyses of onychomycosis burden and its treatment in the female sex are sparse.

With this in mind, we present a narrative review of the existing literature on epidemiology, quality of life (QoL), clinical trial participation, and treatment success in female patients with onychomycosis. We also present real-world data of relevance to onychomycosis in female patients, including prescription patterns by sex for antifungals approved in the United States (US) for onychomycosis treatment, and the impact of nail polish on the efficacy of topical antifungals used for onychomycosis therapy.

PREVALENCE

Global prevalence of onychomycosis has been estimated to be approximately 5.5 percent.⁸ Onychomycosis prevalence in females, however, is difficult to estimate, as reported rates vary greatly. For example, per 11 articles primarily published in the last decade from which female prevalence could be calculated, rates ranged from 4 to 80 percent.^{9–19} Design differences in these hospital-based studies—including study location, study duration (months to years), patient numbers (hundreds to thousands), and patient populations—could contribute to this variability. As expected, some of the highest female prevalence rates (16–80%) were reported in studies of patients with clinical suspicion of onychomycosis or those referred to mycology, with male-to-female prevalence ratios ranging from 0.84 to 1.72.^{9,10,14–16,18,19} Intermediate female prevalence rates (10%¹⁷ and 29%¹²) were from patients visiting dermatology offices for any condition, and the male:female prevalence ratio was slightly below 1.0. Finally, the lowest female prevalence rates were in studies that excluded those seeking help for a fungal foot disease (4%¹¹ and 9%¹³; male:female prevalence ratio of approximately 2) (Figure 1).

The sex differences noted above are unlikely to be due to selection bias, as nine of these 11 studies had a preponderance of females (>50%). The prevalence ratios above are also in line with a systematic review of hospital- and population-based studies from the 1960's through the early

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2000's, which reported a mean male:female ratio of 1.4 (range: 0.44–3.02).²⁰ Male sex was also associated with onychomycosis in a recent analysis of 121,386 outpatients with continuous insurance coverage.²¹ The basis for the lower prevalence in females is not clear and warrants further investigation. Some suggest that occupational factors may play a role, with increased use of occlusive footwear and more frequent nail injuries contributing to a higher incidence of onychomycosis in males.²² Differences in hormone levels between males and females also may result in different capacities to inhibit the growth of dermatophytes.^{22–24} For example, progesterone binds to and inhibits growth of the dermatophytes *Trichophyton mentagrophytes* and *Trichophyton rubrum* *in vitro*.^{24,25} Human androgenic hormones can also differentially inhibit the growth of dermatophytes.²⁶ How these sex hormones function *in vivo* to potentially impact fungal infection seen in onychomycosis is yet to be determined. Finally, differences in nail physiology described below may also help explain this sex difference in onychomycosis prevalence.

PHYSIOLOGY

The nail unit is a dynamic structure, with new growth of fingernails and toenails occurring at a rate of 2–3mm and 1mm per month, respectively.²⁷ Reports on nail growth rates varying by sex are conflicting, with the bulk of studies on the topic published in the early- to mid-20th century suggesting no difference in nail growth rate between males and females.^{28–32} While contemporary literature on nail growth is sparse, one study in which patients self-measured nail growth demonstrated that monthly nail growth rates are slightly faster in healthy, adult American males compared to females (+0.38 [fingernail] and +0.20mm [toenail] per month in males vs. females), although this difference was not statistically significant.³³

Nail composition varies between the sexes. Both toenails and fingernails are thicker in males compared to females.^{34,35} Nail plate and matrix volume is also higher in males than females.³⁶ Male nails have a higher content of disulfide bonds in the α -keratin protein, rendering their fingernail plates stiffer than those of females.³⁷ Such physiological differences in nail biology between males and

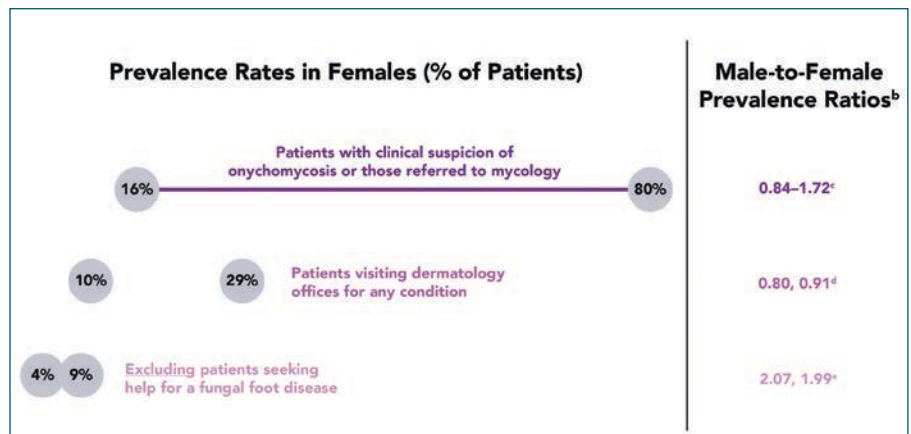


FIGURE 1. Onychomycosis prevalence in females.^a
^aStudy population indicated in purple. Studies primarily spanned 2012–2022. ^bMale-to-Female ratio >1 indicates higher prevalence in males. ^cFrom 7 studies.^{9,10,14–16,18,19} ^dFrom 2 studies.^{12,17} ^eFrom 2 studies.^{13,11}

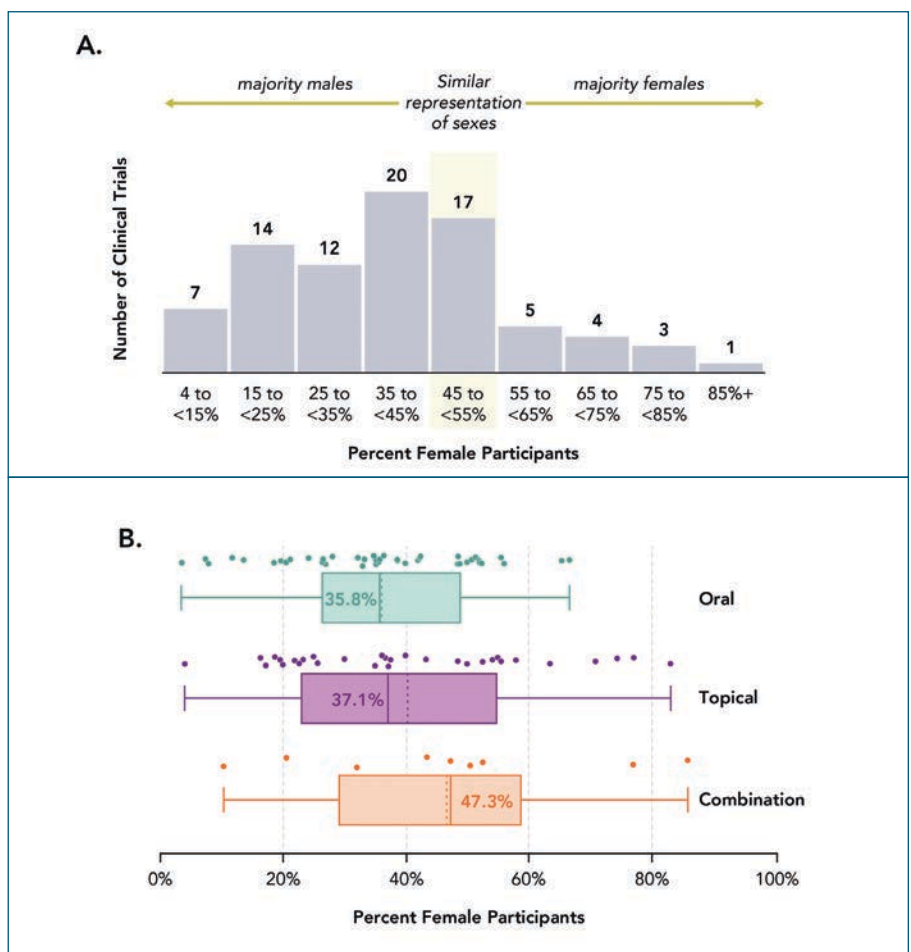


FIGURE 2. Female representation in 83 onychomycosis studies. A) Histogram shows the number of clinical trials based upon the percentage of female participants. B) Box and whisker plots of the percentage of female participants by drug route of administration evaluated (oral, topical, or combination of oral+topical). Figure shows min/max, quartiles, median values (solid line within the box and value shown), mean values (dashed line within the box), and values from individual studies (solid dots).

females may influence treatment success in a sex-specific manner.

CLINICAL TRIALS

In general, women and racial/ethnic minorities remain underrepresented in clinical trials in the US despite efforts to diversify research cohorts.³⁸ To determine if this underrepresentation extends to clinical trials for onychomycosis, we analyzed studies of oral only, topical only, or oral and topical antifungal combination therapies for onychomycosis treatment. A literature search on PubMed for onychomycosis randomized controlled/clinical trials was performed on January 9, 2022. Keywords “onychomycosis,” “clinical trial,” and “randomized controlled trial” were used. Studies not reported in English and those using laser/procedural based therapies were excluded. The following data were extracted: author, year of publication, antifungal route of administration (oral, topical, or oral and topical combination), total number of patients, and number of patients by sex. The percentage of patients by sex was calculated using the N values reported.

Of 102 studies evaluated (see Supplemental Tables 1 and 2, which can be found on the online version of this article), 83 (81%) reported participants' sex, and just over a third of all subjects were female (7,121 of 19,994 [36%]). On average, the clinical trials skewed male with respect to sex demographics (Figure 2A–B). In 43 oral-only trials, female participants comprised an average of 36.0 percent (median: 35.8%) of participants across the studies, with an average male:female ratio of 1.77. In 31 topical-only trials, female participants comprised 40.4 percent (median: 37.1%) of the total, with a male:female ratio of 1.47. In nine combination oral-topical trials, female participants comprised 46.7 percent (median: 47.3%) of the total, with a male:female ratio of 1.14. The male:female onychomycosis prevalence ratios from studies over the last 10 years range from 0.8 to 2.07, suggesting the sex demographics in onychomycosis clinical trials appropriately mirrors onychomycosis prevalence reported in the literature.

QUALITY OF LIFE

QoL impairments due to onychomycosis generally impact females more than males.^{39–48} Early studies, published in the late 1990s, demonstrated that compared with male

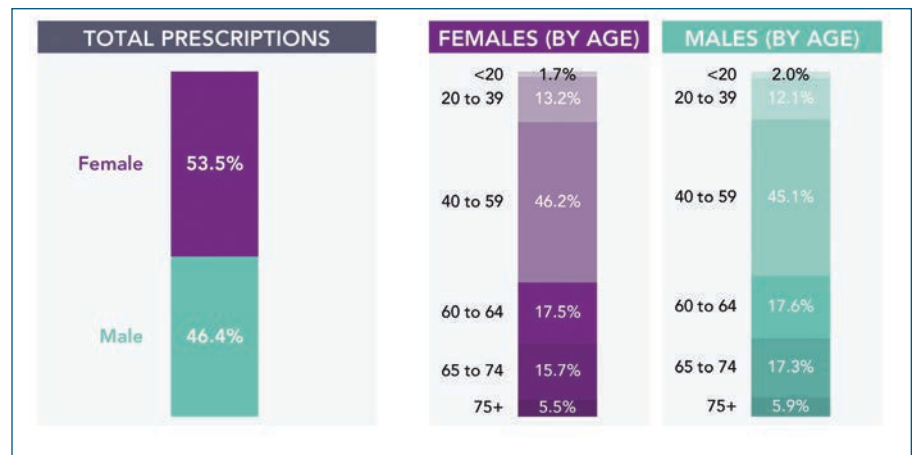


FIGURE 3. Efinaconazole 10% (Jublia[®]) total prescriptions by sex during a six-year period.^a Data for “unspecified” sex (totaling 0.02% of all prescriptions) not shown.
^aJune 2016 to May 2022.

patients, female patients rated their toenail symptoms as more bothersome.^{40,41} Females also reported greater pain in their toes and nails, plus greater problems with appearance of their nails and with performing physical activities compared to males.⁴¹ Social problems, burden of symptoms, and/or emotional state impairments are more pronounced in females than in males.^{45,47} Mean scores on the Dermatology Life Quality Index (DLQI) questionnaire were also numerically higher for females compared to males (6.97 vs. 5.73), indicating poorer QoL.⁴³

While antifungal treatments for onychomycosis are associated with QoL improvements,⁴⁶ there is limited information on potential differences between the sexes. A post-hoc analysis of two Phase III efinaconazole 10% studies found that improvements in QoL were greater in female participants compared to males.²² Scores across all items on the OnyCOE-t questionnaire were lower (worse) in females at baseline (range: males 50.1–72.0, females 32.0–64.9), with greater change from baseline to week 52 (range: males 8.4–26.1, females 12.7–36.0).

TREATMENT EFFICACY IN FEMALES

Onychomycosis treatment efficacy in females is challenging to examine because it is rarely reported in the literature. Of the antifungal drugs approved by the US Food and Drug Administration for the treatment of onychomycosis, analyses by sex have been published for efinaconazole 10% solution (6 publications),^{22,49–53} tavaborole 5% solution

(1),⁵⁴ oral itraconazole (3),^{55–57} and oral terbinafine (3).^{4,56,57} Although the definition of treatment success varied by study, success of onychomycosis treatment was generally greater in women than in men.

Approval of efinaconazole 10% solution was based on two multicenter, double-blind, vehicle-controlled Phase III studies (N=1655), in which 74 to 80 percent of participants were male.⁵⁸ Though baseline clinical characteristics were similar between male and female participants in the Phase III studies,²² females had higher treatment responses. Following 52 weeks of treatment, complete cure rates were significantly higher in females versus males (27% vs. 16%; $P=0.001$)^{50,52} and mean percent affected target toenail was lower (14.4% vs. 20.6%; P value not reported).⁴⁹ Of 19 participants treated with efinaconazole that were completely cured at Week 24, the majority (12/19; 63%) were female.⁵¹ In a Japanese study evaluating efficacy of efinaconazole 10% solution with long-term use for up to 72 weeks (N=219; 66 females), subgroup analysis revealed that treatment success was higher in female compared to male patients (62% vs. 54%; P value not reported).⁵³

Female onychomycosis patients in the tavaborole 5% solution arm in Phase III studies (N=1194, 148 females) saw notable improvements in the appearance of their nail plates over time.⁵⁴ Nails from tavaborole-treated females had significantly greater increases in the percentage of normal nail (one measure of an improved onychomycosis

infection) from baseline to end-of-study at 52 weeks as compared to vehicle-treated nails (31.9% and 7.9%, respectively; $P < 0.001$). In the tavaborole-treated females with more than 50 percent baseline nail plate infection, there were significantly greater increases in normal nail from baseline to end-of-study as compared to patients with 50 percent or less baseline infection (80.9% and 22.4%, respectively; $P < 0.0001$).

For oral antifungals, analyses of treatment success by sex yielded mixed results, with some showing that females were more likely to achieve cure whereas others saw no effect of sex on efficacy outcomes. In a trial comparing continuous terbinafine with intermittent terbinafine in onychomycosis (N=199, 47 females), women were more likely than men to reach clinical cure (defined as a nail without any clinical signs of onychomycosis; odds ratio for males not achieving clinical cure: 2.558 [1.168–5.606]).⁴ In an analysis of 81 patients (61 females) with onychomycosis due to nondermatophyte molds or *Candida* in whom treatment with either terbinafine pulse or itraconazole pulse was completed, 51 percent of females versus 15 percent of males were “cured,” with male sex, but not female sex, having significant negative effects on cure rates ($P < 0.01$).⁵⁶ In a study comparing continuous terbinafine with intermittent itraconazole (N=496, number by sex not reported), univariate prognostic factor analysis showed that no baseline clinical parameter, including sex, had a statistically significant association with mycological cure at 72 weeks.⁵⁷ Nine months following 4-month treatment with itraconazole in a study of 24 patients (12 females) with onychomycosis, sex of the patient was not correlated with clinical and mycological outcome at the end of the study.⁵⁵

A caveat to comparing female-specific efficacy results across studies and antifungals is that definitions of success, study populations, disease severity, drug doses, treatment time, and follow up period vary widely. However, available data still suggest that oral and topical antifungals are efficacious in female patients with onychomycosis, and in some instances, efficacy is greater in females compared to males. While the reason for this is unknown, this may be explained, to some degree, by the physiological differences in nail biology between the sexes noted above.

REAL-WORLD TREATMENT OF ONYCHOMYCOSIS IN FEMALES

Prescription patterns. Although onychomycosis prevalence generally appears to be greater in men, women represent approximately half or more of patients seeking help or treatment for infected nails. More female patients (57.6% vs. 42.4% male) made visits to physicians' offices in the US for a possible diagnosis of onychomycosis during an 18-year period from 1993–2010, per the National Ambulatory Medical Care Survey database.⁵⁹ In the UK between the years 2001 and 2017, a slightly higher proportion of males compared to females (52% vs. 48%) sought treatment for onychomycosis from their general practitioner.⁶⁰ To explore the treatment of females with onychomycosis in the real world, we analyzed prescription patterns by sex of a commonly used topical antifungal (efinaconazole 10%; Jublia®, Ortho Dermatologics). During the six-year period analyzed, 53.5 percent of prescriptions for topical efinaconazole were to females, indicating that females account for slightly more topical efinaconazole prescriptions than males. (Figure 3).

Topical efficacy in onychomycosis nails treated with polish. Real world treatment of onychomycosis in females is further complicated by the fact that female patients may wish to use nail polish to camouflage nail changes associated with onychomycosis. In clinical trials of topical efinaconazole 10%⁵⁸ and tavaborole 5%,⁶¹ participants were instructed to not apply nail polish,⁶² such restrictions in the real world may hamper treatment of female patients with onychomycosis.⁶² Therefore, it is important to understand the compatibility and efficacy of topical antifungals in individuals wearing nail polish, though data on the subject are limited.

Only one study has evaluated the impact of tavaborole 5% solution on nail polish,⁶³ though there are no studies on nail penetrance or clinical efficacy of tavaborole 5% in patients with onychomycosis who concurrently use nail polish. Efinaconazole 10% solution may impact the appearance of nail polish.^{63,64} However, other data on its compatibility with nail polish are promising. Nail polish did not affect penetrance of efinaconazole 10% through human cadaver nails,⁶⁵ or clinical efficacy of efinaconazole 10%—measured by onychomycosis severity index, and nail growth and thickness—in patients with onychomycosis.⁶⁴

CONCLUSION

There is a paucity of published studies analyzing the impact of onychomycosis on female patients. For reasons that are not well understood, onychomycosis prevalence and the efficacy of current treatments appear to be different in females compared to males. There is a need for more studies assessing real-world factors that may affect treatment of onychomycosis in females, especially the compatibility and efficacy of topical antifungals with concurrent nail polish use. A more thorough understanding of factors that impact onychomycosis development and treatment in females could help mitigate the significant QoL burden experienced by female patients with onychomycosis.

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