Application of Nail Polish During Topical Management of Onychomycosis

Are Data Available to Guide the Clinician About What to Tell Their Patients?

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ABSTRACT

Topical antifungal management of toenail onychomycosis has been fraught with several therapeutic challenges including difficulty gaining access to the site of infection and the need for prolonged durations of therapy. In addition, there has been a marked lack of information on the impact of toenail polish application on drug penetration after application. This article reviews available data from studies evaluating the effect of nail polish on antifungal drug penetration using *ex vivo* laboratory models with cadaver fingernail plates with both tavaborole 5% solution and efinaconazole 10% solution. In addition, changes in nail polish appearance and color transfer to applicators are also discussed, with changes noted with topical efinaconazole. Importantly, there are no data on whether or not nail polish application alters the efficacy of these topical agents.
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Management of toenail onychomycosis (T-ON) continues to be a major therapeutic challenge, primarily related to the physical characteristics of the nail unit, the slow growth of the nail plate, the prolonged durations of treatment that are usually required to achieve clearance or marked improvement of infection, and the frequency of incomplete clearance and recurrence.[1,2] Additionally, cure rates reported with standardized therapeutic regimens that are approved by the United States Food and Drug Administration (FDA) for dermatophyte T-ON show that although some cases are cleared or markedly improved at the usual 12-month study endpoint, many cases of onychomycosis persist despite the use of therapy as defined in the study protocols.[3–6] Because it may take several weeks to at least a few months before visible improvement in T-ON occurs after initiation of therapy with an oral or topical agent, adherence with treatment is extremely important as patients may easily be discouraged if they do not perceive improvement relatively soon after starting treatment.

The more recent availability of two new topical agents that are FDA approved for treatment of dermatophyte T-ON, tavaborole 5% solution and efinaconazole 10% solution, have provided additional therapeutic choices, especially in cases of mild-to-moderate severity. The pivotal clinical trials with these agents included once-daily application for 48 weeks without adjunctive nail plate debridement.[4–8] Importantly, inclusion in the study mandated that subjects could not utilize other nail products including nail polish throughout the duration of the trial and were required to refrain from pedicures.[7,8] Nail trimming was completed at the study sites by designated staff during visits according to the standards allowed within the FDA-approved study protocols. Therefore, there are no data based on clinical trials that provide adequate information about the efficacy of these agents when nail polish is used. Nevertheless, clinicians in "real world" practice encounter primarily female patients who wish to use nail polish to camouflage unsightly nail changes associated with T-ON. This scenario can impact

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dramatically on whether or not patients choose to proceed or comply with topical treatment.

Although exclusions and restrictions are mandated in study protocols, in clinical practice clinicians see "all comers" with T-ON, which includes a wide range of ages, disease severities, comorbid conditions, and psychosocial considerations. Many women express a personal desire to camouflage the condition as best as possible in order to be able to wear open shoes or expose their feet in appropriate social situations. This paper reviews available data on application of nail polish in conjunction with topical application of either tavaborole 5% solution or efinaconazole 10% solution, assessing primarily penetration and permeation characteristics and qualitative appearance of polished nail plates. Application and testing methodologies are explained, primarily using *in vitro* and *ex vivo* models. It is important to recognize from the outset that data from clinical trials on efficacy of treatment of T-ON with either of these topical agents in subjects applying nail polish are not available. The data are presented to inform the clinician on what is reported to date to assist in clinical decision making and in educating patients as best as possible, especially those who are emphatic about wanting to use nail polish during treatment. Efficacy, tolerability, and safety of topical application of tavaborole 5% solution and efinaconazole 10% solution for treatment of T-ON are discussed elsewhere.[5–8] This paper discusses data related to penetration of the nail unit with these two topical antifungal solutions with emphasis on application in the presence of nail polish, and the effects of application of either topical agent on the appearance of polished nails and/or removal of nail polish.

TAVABOROLE 5% TOPICAL SOLUTION

Tavaborole is an oxaborole antifungal agent that interferes with fungal protein synthesis by inhibiting the editing domain of cytoplasmic leucyl-transfer ribonucleic acid (tRNA) synthetase.[9] This mechanism of antifungal activity is unique among currently available topical and oral antifungal agents, including azoles, allylamines, and hydroxypyridones.[10] Available as a 5% solution formulation (Kerydin, PharmaDerm, Princeton, New Jersey), once-daily application of tavaborole 5% solution is FDA approved for the topical treatment of dermatophyte T-ON caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.[5] The low surface tension of the solution, formulation, small molecular size, and favorable keratin binding characteristics of tavaborole are all believed to be optimal for transungual and subungual penetration of the drug to the predominant sites of fungal infection in T-ON.[5,7] An *in vitro* study using cadaver donor fingernails compared tavaborole 5% topical solution and ciclopirox 8% solution, each applied to separate nail plates for 14 days. The results showed a 40-fold greater mean cumulative nail penetration of tavaborole as compared to ciclopirox ($P<0.004$).[11]

Assessment of human fingernail penetration of tavaborole 5% topical solution through nail polish. Two studies were completed evaluating the *in vitro* penetration of tavaborole, formulated as a 5% topical solution, through nail polish on *ex vivo* fingernails using the Franz Finite Dose *In Vitro* Permeation Test Model.[12] Application was completed to non-diseased fingernails procured from human cadaver donors. One study incorporated application to nail plates coated with a single layer of designated nail polish (Study 1-T5) and the second study with multiple layers of designated nail polish (Study 2-T5).

Methodology. The methodology used was standardized and completed based on recognized good laboratory practices.[12] Each fingernail was mounted on a diffusion cell, which was secured so that the undersurface of the nail plate was in contact with a receptor fluid bath in order to collect any study solution that penetrated into and permeated through the nail plate; all were maintained steadily at proper temperature. The securing method assured that the applied solution did not gain direct access into the receptor fluid bath. Modified Franz diffusion cells were used in Study 1-T5 and vertical diffusion cells were used in Study 2-T5. After prepping of the nail plates to remove any unwanted debris, the polished nails were coated with the type of nail polish and the number of layers as defined in the study protocol. With each daily application of tavaborole 5% topical solution, a finite dose was evenly applied to the top surface of the nail plate. Before properly timed changing of the receptor bath fluid each day, quantity-defined aliquots were collected daily at the same time (at approximately 24 hours after each applied dose) over the duration of the study and analyzed using a recognized quantification method (LC/MS/MS in Study 1-T5; high performance liquid chromatography [HPLC] in Study 2-T5). Throughout the study, the diffusion cells containing the nail plates and the receptor fluid baths were maintained at a steady temperature designed to represent *in vivo* conditions as closely as possible. The phosphate buffered isotonic receptor bath solution was selected as it was shown to maintain the stability of tavaborole.

Single Nail Polish Layer Study (Study 1-T5). Five non-diseased fingernails were obtained from four individual human female cadaver donors (N=20 fingernails).[12] Baseline characteristics of nail plate thickness (cm) and nail plate density (gm/cm^3) were captured in order to complete analysis of study results. Three randomized study groups were defined.[12] Group 1 included two fingernails from each donor, which were polished with a single layer of a commonly available nail polish (L'Oreal brand red nail polish) and later underwent application of a finite amount of tavaborole 5% topical solution (12µL/cm^2) once daily for 20 consecutive days. Group 2 included two fingernails from each donor that were left unpolished and later underwent application of tavaborole 5% topical solution for 20 consecutive days. Group 3 served as a control group with one fingernail from each donor left unpolished and not treated with study drug solution. After determination of concentrations within the receptor fluid were analyzed, calculations of the flux rate and cumulative penetration of tavaborole through human fingernail plate were calculated

for each study group. The within donor means of nail penetration of tavaborole were averaged to obtain a population mean with standard deviations for each study group.

The results for Study 1-T5 are depicted in Figure 1 and are summarized as follows.[12] The mean cumulative tavaborole nail penetration after application of tavaborole 5% topical solution for 7 days, 14 days, and 20 days was numerically and progressively higher in the study group undergoing application to polished nail plates. After 20 days of application, the cumulative tavaborole penetration levels in the polished nail plate group averaged 3.5±1.4mg/cm^2 as compared to 2.7±1.3mg/cm^2 in the group with unpolished nail plates. Presence of a single coat of a specified brand of red nail polish did not impair the *in vitro* penetration of tavaborole into human fingernail plates and appeared to potentially enhance penetration into and permeation through the nail plate (Figure 1). Analysis of fingernail plates also confirmed the penetration of tavaborole into the nail plate supporting transungual penetration of the drug.

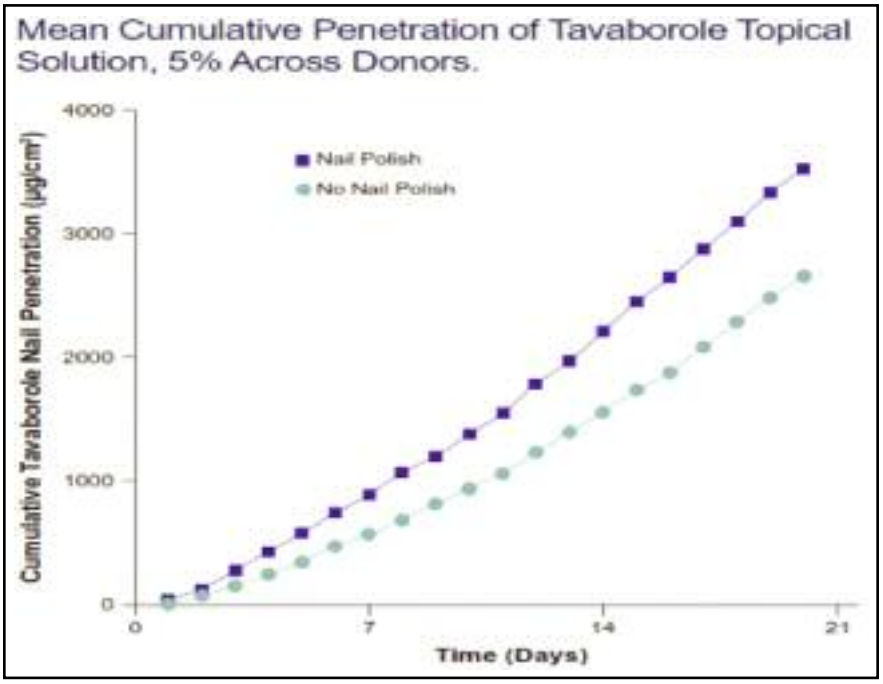

Figure 1. Topical tavaborole 5% solution penetration through one coat of nail polish.[12] Study 002-NCL PK-070-01, Anacor Pharmaceuticals, Inc., 2013. Mean results from dated compiled from 8 polished and 8 unpolished non-diseased human cadaver nail plates.

Multiple Nail Polish Layer Study (Study 2-T5). Using testing methodology similar to Study 1-T5 with some modifications, the *in vitro* penetration of tavaborole from the 5% topical solution was evaluated after application on *ex vivo* polished versus non-polished, non-diseased, human fingernail plates procured from eight female cadaver donors (N=28 fingernails). However, the protocol in this study (Study 2-T5) differed markedly from Study 1-T5.[12] Five study groups were defined and randomized in order to assess different nail polish application practices.[12] Group 1 received four coats using a designated nail salon brand polish (OPI Cocoa Shade [Cocoa a Go Go]); one base coat, two standard coats of colored polish, and one clear topcoat). Group 2 received one coat of the same designated salon brand polish. Group 3 received two coats of a designated commercially available home (over the counter [OTC]) brand nail polish (L'Oreal Devil Wears Red [J500]). Group 4 received one coat of the same designated commercially available home (OTC) brand nail polish. Group 5 fingernails remained unpolished (control group). A finite amount (25µL/cm^2) of tavaborole 5% topical solution was applied to each nail plate at the same time on 14 consecutive days. Determination of concentrations within the receptor bath fluid were analyzed using the proper timing as described above, calculations of the flux rate and cumulative penetration of tavaborole were completed, and nail penetration levels of tavaborole were averaged to obtain a population mean with standard deviations for each study group.

The results for Study 2-T5 are depicted in Figure 2 and are summarized as follows.[12] A comparison of results from all study groups showed that the mean cumulative tavaborole penetration was numerically and progressively higher in the groups with polished nails compared with the unpolished control nail plates when evaluated after 7 days and 14 days of study drug application. Evaluation at Day 14, after daily application of tavaborole 5% topical solution for 14 days, showed the following mean cumulative penetration levels: 1.2±0.6mg/cm^2 with four coats of salon brand nail polish, 1.2±1.0mg/cm^2 with one coat of salon brand nail polish, 1.5±1.3mg/cm^2 with two coats of home (OTC) brand nail polish, 1.4±0.8mg/cm^2 with one coat of home (OTC) brand nail polish, and 0.6±0.3mg/cm^2 with the unpolished control nail plates. The study outcomes show that tavaborole, administered as a 5% topical solution once daily, was capable of penetrating up to four coats of nail polish and that presence of nail polish did not impair tavaborole penetration (Figure 2). As in Study 1-T5, presence of nail polish appeared to potentially increase tavaborole penetration into and permeation through the tested fingernail plates. Study 2-T5 used both a salon brand and a home (OTC) brand of nail polishes. The differences in the numerical results of mean cumulative nail penetration of tavaborole between Study 1-T5 and Study 2-T5 may potentially be explained by some differences in study design, characteristics of individual nail plates used in the studies, and the modifications in testing methodology used in Study 2-T5.[12]

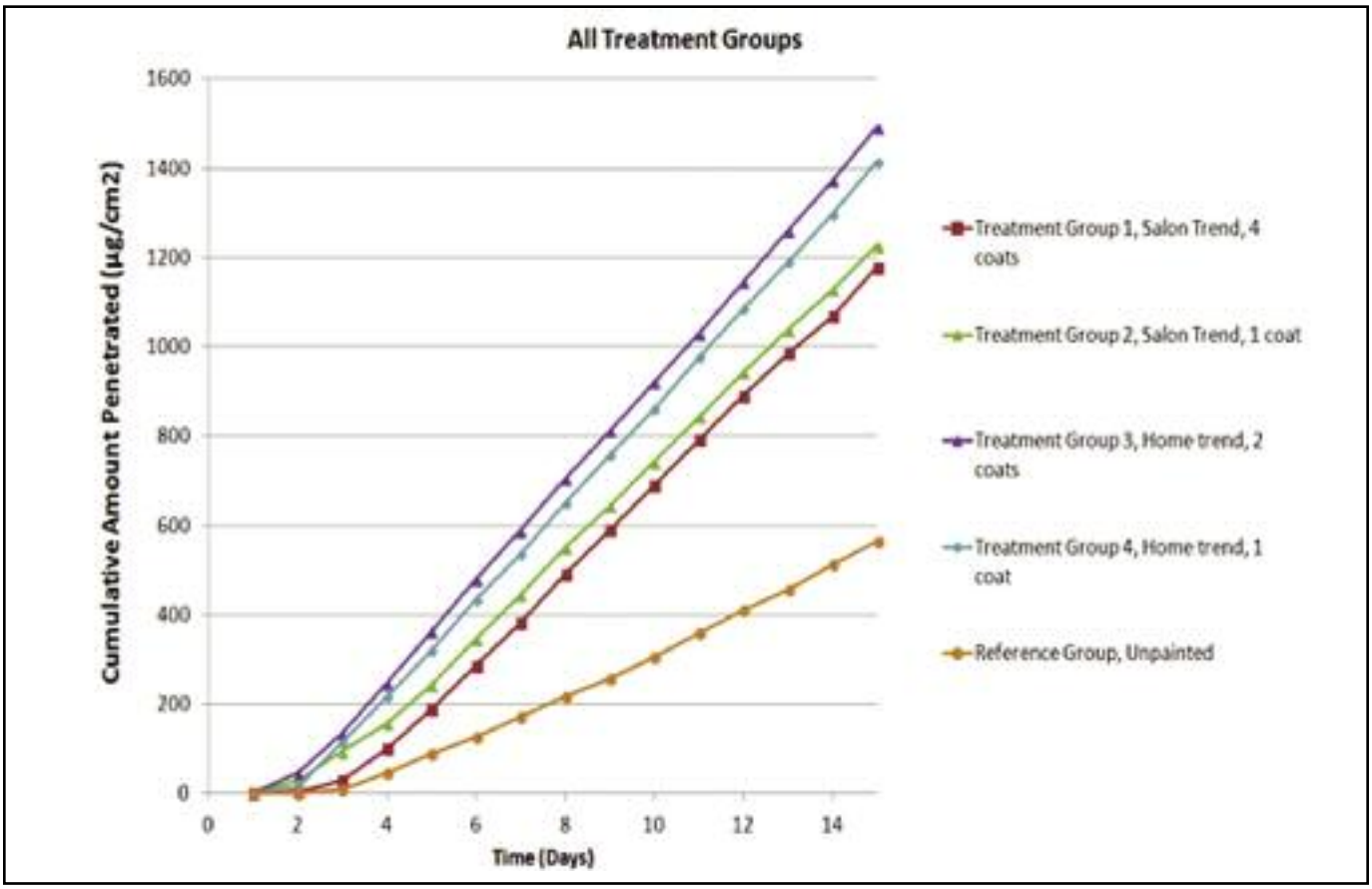

Figure 2. Topical tavaborole 5% solution penetration through multiple coats of nail polish.[12] Study TER-002-14, Anacor Pharmaceuticals, Inc., 2013. Study completed using non-diseased, human fingernail plates procured from 8 female cadaver donors (N=28 fingernails).

EFINACONAZOLE 10% TOPICAL SOLUTION

Efinaconazole is an imidazole antifungal agent formulated as a 10% solution (Jublia, Valeant Pharmaceuticals North America LLC, Bridgewater, New Jersey) that is FDA-approved for once-daily topical treatment of dermatophyte T-ON caused by *T. rubrum* or *T. mentagrophytes*.[6,8] The low surface tension of the solution formulation combined with the antifungal activity and keratin binding properties of the molecule have been reported to be advantageous in the treatment of T-ON.[8,13] Nail concentrations of efinaconazole were determined as part of a multicenter, open-label study of subjects with T-ON (N=40) following repeated applications of efinaconazole topical solution (5% and 10%) to the toenails over 28 days followed by a final assessment at two weeks post-treatment.[13] Efinaconazole nail plate concentrations were fourfold higher than minimum inhibitory concentration (MIC) values of efinaconazole against dermatophytes and were not affected by dystrophic nail changes and thickness differences associated with T-ON in the cases evaluated. As with tavaborole 5% topical solution, the efficacy and safety of daily application of efinaconazole 10% topical solution for dermatophyte T-ON over 48 weeks have been confirmed in pivotal studies including Phase 3 trials submitted to the FDA.[5–8] Importantly, as with tavaborole 5% topical solution, clinical efficacy of efinaconazole 10% topical solution in the treatment of polished nails affected by T-ON has not been studied. The following reviews *in vitro* evaluation of the nail penetration of 14C-labeled efinaconazole (5%) after application to polished as compared to unpolished non-diseased human thumbnails using a human cadaver nail model.[14]

Assessment of human thumbnail penetration of efinaconazole through nail polish. *Methodology.* Non-diseased thumbnail plates were obtained from multiple human cadaver donors; in order to control for proper comparisons of results obtained from different nail plates, analyses of plate size and thickness were completed to assure sample-to-sample consistency.[14] After standardized preparation, each test nail plate was polished with one of three commercially available nail polishes with two coats of polish applied (Dior 999 Red Royalty; Essie 488 Forever Yummy; Revlon 550 Cherry) and stored in their respective study chambers. A set on uncoated nail plates was left unpolished to serve as a control. A solution of quantified 14 C-radiolabeled efinaconazole was prepared to achieve a final concentration of 5% efinaconazole. A finite dose (0.15 uCi/dose) of efinaconazole solution was applied to tested

nail plates on Days 1, 2, 3, 4, and 7. After Day 7, nail polish and any efinaconazole solution present on the nail surface that had not penetrated the nail plate was removed. The tested nail plates were then dissolved in a tissue solubilizer to create a receptor phase allowing for analysis of the concentrations of efinaconazole that penetrated into each nail plate, with statistical analyses performed on the resultant data.[14]

The results were as follows (Figure 3).[14] After application on Day 7, 0.56% of the applied dose of efinaconazole was shown from the control group of unpolished nail plates, although some large variations required rejection of clearly identifiable outlier data points for statistical analysis. The reported permeation rates obtained from nails polished with the Essie, Revlon, or Dior nail polishes were 0.43%, 0.50% and 0.51% of the applied efinaconazole dose, respectively (Figure 3). Overall, the authors concluded that nail polish did not inhibit the penetration (permeation) of efinaconazole in tested nail plates under the study conditions used. Cumulative concentrations of efinaconazole in the receptor phase at the end of the study (Day 7) ranged from 13.6 to 17.6µg/cm^2. The authors did note that after the first application of efinaconazole solution, nail polish color was observed on all brush applicators, especially with the Essie nail polish. Additionally, tackiness of nail polish was present after drying of the efinaconazole solution and increased progressively with repeated applications.[14] Brush application of efinaconazole 10% solution to polished *ex vivo* human cadaver nail plates has been shown to alter polish appearance and transfer color to applicator tips (see below).[15] In patients applying efinaconazole 10% solution to toenails using the recommended application of a single focus (drop) to the central nail plate and brush application to the hyponychium and lateral nail folds, combinations of nail polish brands, colors, top coats, and top coat plus base coats were evaluated.[16] Touching the application brush directly to polished toenail plate when applying efinaconazole 10% solution produced visible alteration (damaged appearance) of polish on the surface of the plate. A single coat of nail polish lasted in appearance for 1 to 2 days after efinaconazole application, for 3 to 7 days with colored nail polish and a top coat, and for up to 14 days with a base coat, colored nail polish, and a top coat. Examples of nail polish brands that were used were Essie, Orly, and OPI; top coats and/or base coats included China Glaze and Revlon. Darker nail polish color tended to be more stable than lighter pigments, and differences in nail plate appearance were noted between brands; China Glaze appeared to provide greater stability among the brands evaluated. It is not known what impact these application methods have on the efficacy of efinaconazole 10% solution in the topical treatment of T-ON.[16]

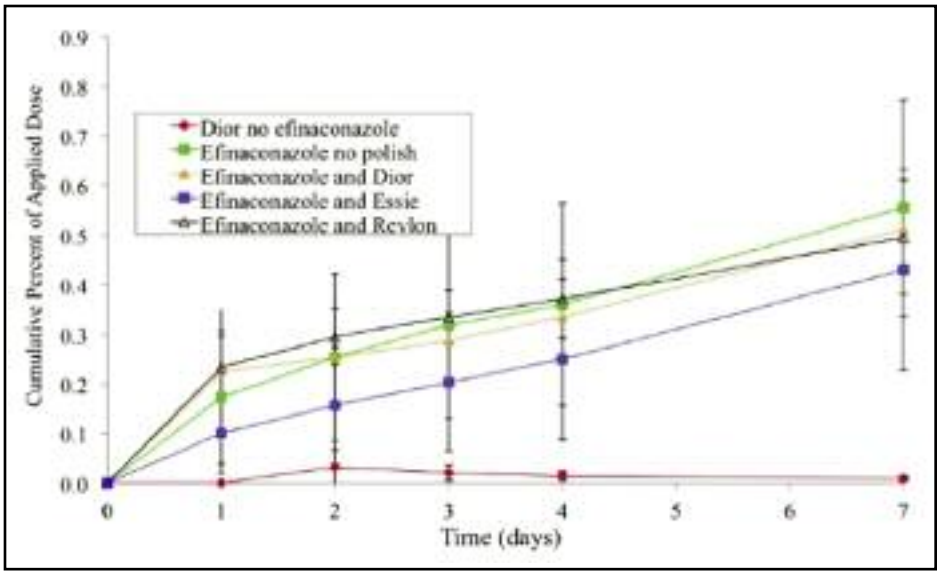

Figure 3. Cumulative permeation of (14C)-efinaconazole solution receptor phase (mean % of applied dose).[14]

APPEARANCE OF NAIL POLISH ON HUMAN FINGERNAILS (*EX VIVO*) AFTER APPLICATION OF TOPICAL TAVABOROLE OR TOPICAL EFINACONAZOLE

A study was completed to evaluate nail polish appearance, polish color transfer to respective applicators, and polish color transfer from respective applicators to remaining drug solution after application of tavaborole 5% solution (n=6) or efinaconazole 10% solution (n=6) to polished *ex vivo* non-diseased human cadaver fingernails once daily for seven days.[15] Unpolished nail plates were also used as controls. Nail plates used in each study group were randomly selected. After the nail plates were appropriately cleaned, they were assessed for length (range 10.02–12.06mm), width (range 9.95–14.39mm), and thickness (0.31–0.85mm). The study drug solutions were applied using their commercial packaging, with tavaborole in a bottle with a dropper applicator, and efinaconazole in a bottle with a non-detachable brush applicator. The following further depicts the study methodology.

- The polished nail plates received two coats of brand red nail polish (L'Oreal Devil Wears Red #420) and were mounted onto a designated foam platform using a specified glue.
- Nail plates were randomly assigned to the tavaborole study arm (n=6) or the efinaconazole study arm (n=6) according to their respective instructions described in their FDA-approved product labeling.
- A subset of applicators (brush tip [efinaconazole]; dropper tip [tavaborole]) was used to apply each study drug solution to a sheet of white watercolor paper each day. This was completed immediately

TABLE 1. Evaluation of appearance of polished nail plates, drug solution applicators, and color transfer from nail polish after application of topical tavaborole or efinaconazole solutions to polished *ex vivo* human fingernails[15]

PARAMETER	TAVABOROLE 5% SOLUTION	EFINACONAZOLE 10% SOLUTION
Appearance of polished nail plates	No signs of discoloration over 7-day study duration; nail polish appeared to dry within minutes after application.	Polished nail plates changed in appearance and were discolored after first application and throughout the 7 days of the study; polished nail plates appeared tacky after application from first day and throughout study
Appearance of applicators	Dropper applicators did not change in appearance/color throughout the study.	White brush applicators changed color to pink/red after the first application and increased with additional applications.
Color transfer	No color transfer was noted from polished nail plates to white watercolor paper or within the remaining solution.	Color transfer from polished nail plates was noted on white watercolor paper and within the remaining solution.

See Figures 4, 5, 6, and 7 for visible illustrations of study outcomes.

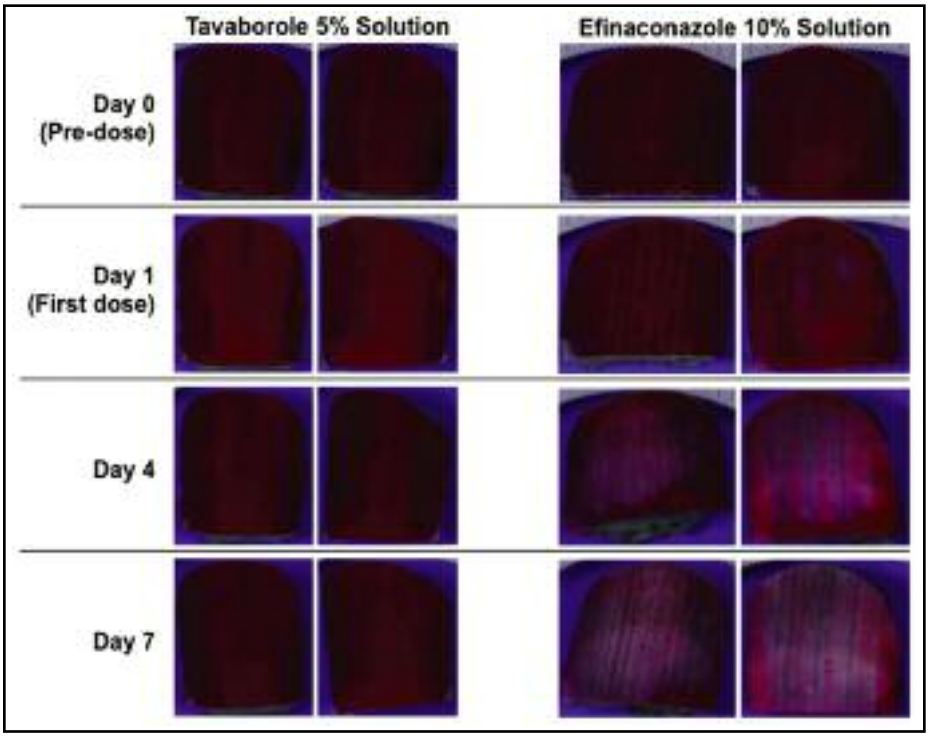

Figure 4. Change in appearance of polished nail plates after application of topical tavaborole 5% solution or efinaconazole 10% solution.[15] Reprinted with permission from: Vlahovic TC, Coronado D, Chanda S, et al. Evaluation of the appearance of nail polish following daily treatment with topical solutions of tavaborole or efinaconazole. *J Drugs Dermatol.* 2016;15:89–94.

after application to the nail plates to evaluate any presence of color transfer from the respective applicators to the paper. A control group for each study drug included applicators applied each day to the watercolor paper only.

- Documentation of changes in appearance of nail plates, used applicators, and tested water-color paper were photographed daily following treatment applications using standardized photographic methodology. At the end of the study, each used bottle of tavaborole and efinaconazole solutions was opened, poured into a clear glass vial, assessed for color differences through comparison with respective bottles of control solution, and photographed for documentation.

Outcomes. The outcomes of this study included evaluation of nail plate appearance, applicator appearance, color transfer to white watercolor paper, and appearance of study drug solution. These results are depicted in Table 1 and illustrated in Figures 4, 5, 6, and 7.

CONCLUDING REMARKS

The information in this article is not presented to encourage the use of nail polish during topical management of onychomycosis. In fact, as stated earlier, there are no efficacy and tolerability data on the topical management of onychomycosis applied to polished nail

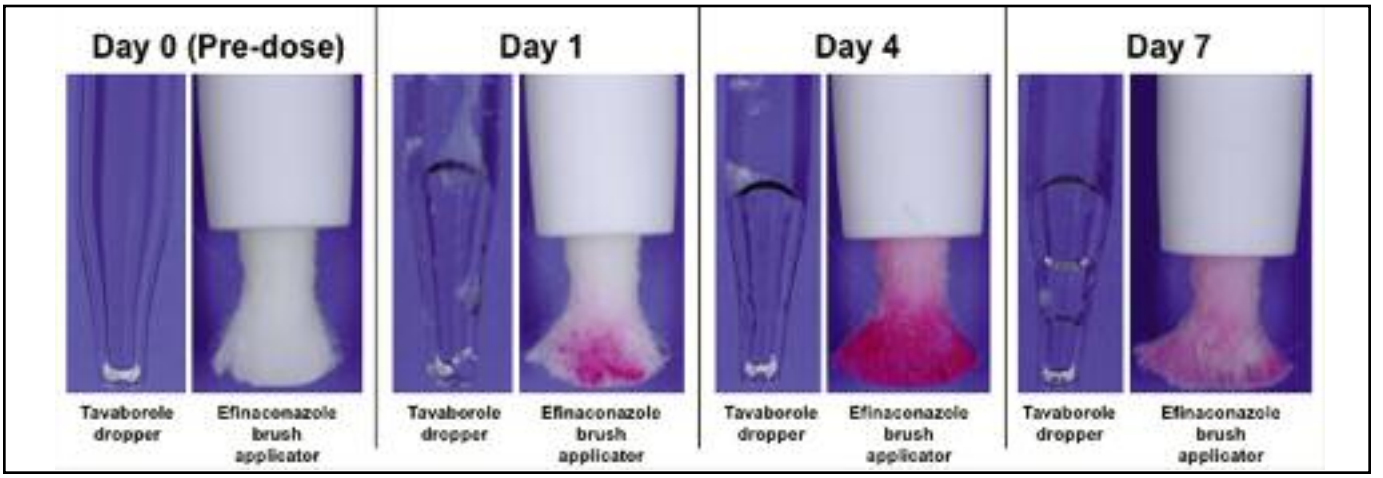

Figure 5. Evaluation of color transfer from polished nail plates. Appearance of tavaborole dropper and efinaconazole brush after treatment application. The polished nail plates received two coats of brand red nail polish (L'Oreal Devil Wears Red #420) and were mounted onto a designated foam platform using a specified glue. Nail plates were randomly assigned to the tavaborole study arm (n=6) or the efinaconazole study arm (n=6) according to their respective instructions described in their FDA-approved product labeling. Representative applicator shown for each study drug solution.[15] Reprinted with permission from: Vlahovic TC, Coronado D, Chanda S, et al. Evaluation of the appearance of nail polish following daily treatment with topical solutions of tavaborole or efinaconazole. *J Drugs Dermatol.* 2016;15:89–94.

plates. Nevertheless, as some patients may choose to apply nail polish during topical therapy for onychomycosis, it is pertinent to review collectively in one source the information that is available to date with both topical tavaborole and topical efinaconazole solutions. An obvious limitation of the studies includes use of *ex vivo* non-diseased human fingernails to assess penetration characteristics. However, the methodologies required would not be practical as they are far too invasive to complete in human subjects. It would also be difficult to accurately assess penetration properties in diseased nail plates as they are likely to differ markedly in morphology and thickness due to the infection.

Nail plate penetration data after topical application of either tavaborole 5% solution or efinaconazole 10% solution using the methodologies discussed above with both polished and unpolished nail plates demonstrated that nail polish did not impair the transungual penetration of either drug. With topical tavaborole, there was some suggestion that penetration was enhanced by the presence of nail polish.

The nail plate appearance and color transfer evaluations do show that topical efinaconazole 10% solution can alter and remove nail polish from the surface of the nail plate and that the polish color is adsorbed on to the brush applicator. Thus, it is important that patients treated with this agent who utilize nail polish be educated about this so they are not surprised by its occurrence. Application of either solution to the hyponychium is important to optimize migration of the antifungal agent into the subungual (onycholytic) space where there is greater access to the nail bed.

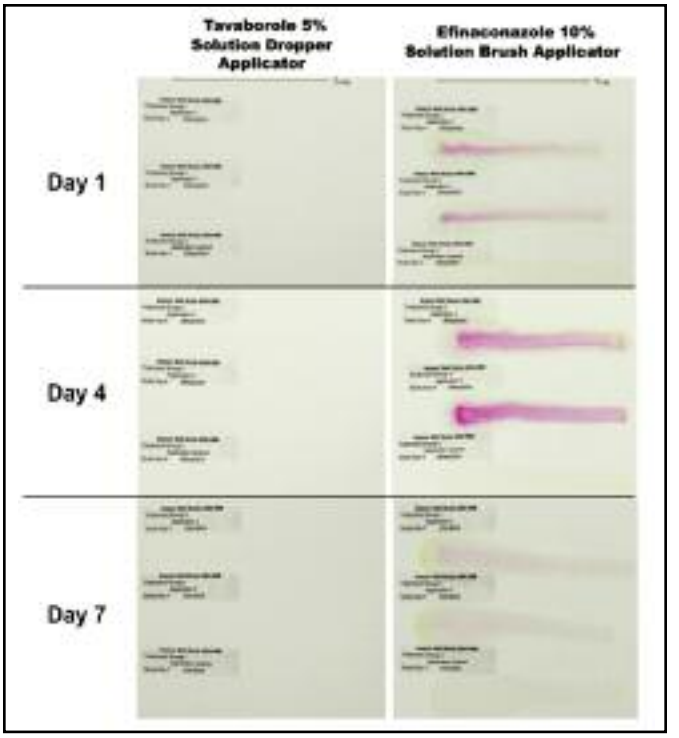

Figure 6. Color transfer to white watercolor paper from applicators after contact with polished nail plates. Subset of applicators evaluated. Brush tip with efinaconazole 10% solution. Dropper tip with tavaborole 5% solution. Selected applicators were used to apply each study drug solution to a sheet of white watercolor paper each day. This was completed immediately after application to the nail plates to evaluate any presence of color transfer from the respective applicators to the paper. A control group for each study drug included applicators applied each day to the watercolor paper only (were not in contact with polished nail plates).[15] Reprinted with permission from: Vlahovic TC, Coronado D, Chanda S, et al. Evaluation of the appearance of nail polish following daily treatment with topical solutions of tavaborole or efinaconazole. *J Drugs Dermatol.* 2016;15:89–94.

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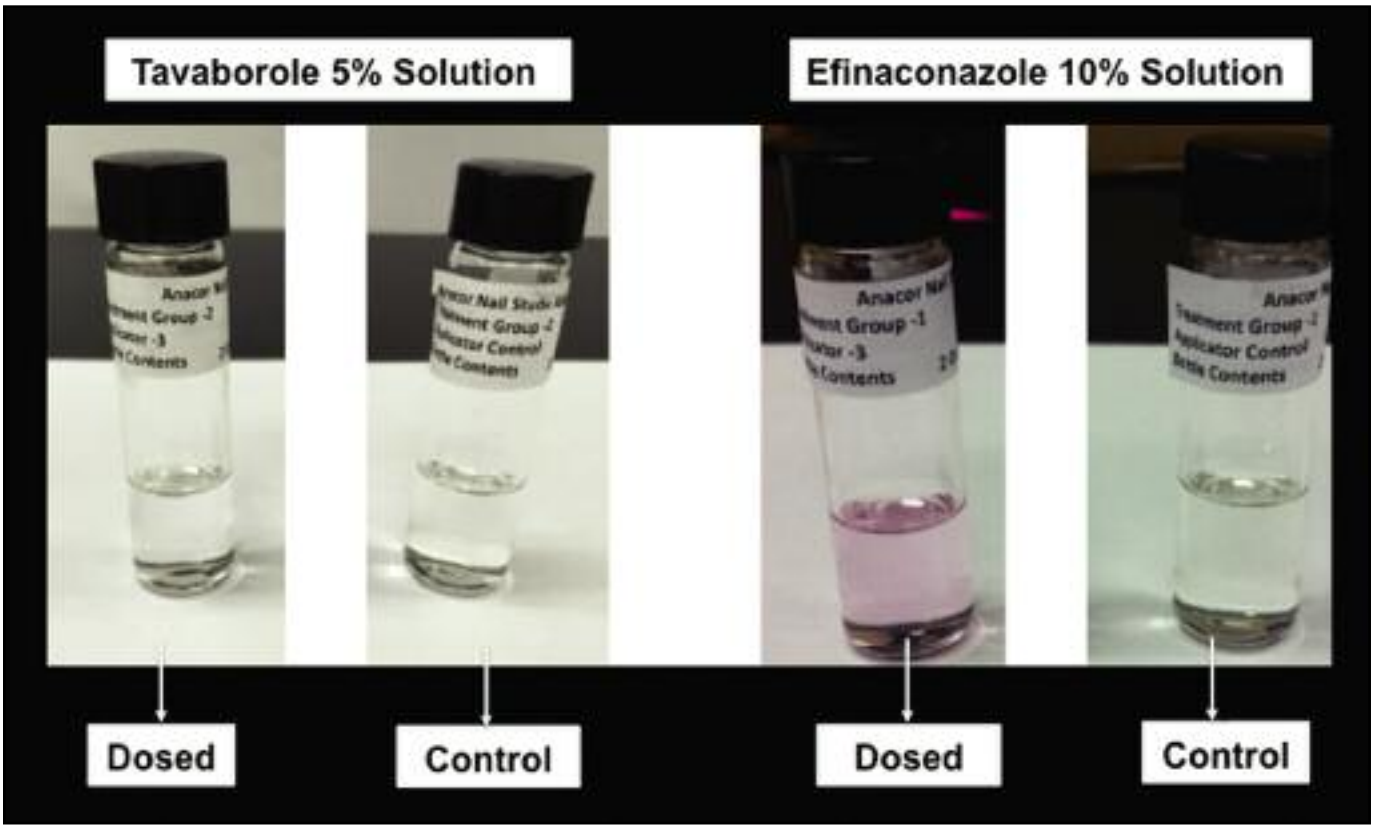

Figure 7. Color transfer from applicators to remaining drug solution in their containers after application to polished nail plates (Day 7).[15] Reprinted with permission from: Vlahovic TC, Coronado D, Chanda S, et al. Evaluation of the appearance of nail polish following daily treatment with topical solutions of tavaborole or efinaconazole. *J Drugs Dermatol.* 2016;15:89–94.

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