UPDATE ON ONYCHOMYCOSIS TREATMENTS

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CONFLICTS OF INTEREST

• Valeant
• Sandoz
• EPI Health
EVALUATION AND TREATMENT ALGORITHM

Onychomycosis

OSI Comorbid Conditions?

OSI severe: orals (multiple courses), with/without adjunctive topical treatment
OSI moderate: orals and/or topical
OSI mild: topical monotherapy

Differential Diagnosis

Appropriate Treatment

OSI, onychomycosis severity index.
1. THE ROLE OF **DERMOSCOPY** IN THE DIAGNOSIS OF DISTAL LATERAL SUBUNGUAL ONYCHOMYCOSIS

- *Arch Dermatol Res. 2018 Jan;310(1):57-69*

- Frequency of patterns seen in DLSO

- Confirmed with PAS and/or culture; then dermoscopy

- Ruin Appearance 92%

- Homogeneous Leukonychia 52.2%

- Punctate Leukonychia 69.3%

- Black discoloration 18%
WHEN TO SELECT A TOPICAL ANTIFUNGAL AGENT

- **MILD – MODERATE** disease
- **ALTERNATIVE** therapy for patients who cannot or will not take an oral antifungal
- Potential **ADJUNCTIVE** therapy along with orals (inside-out/ outside-in) for moderate-to-severe disease
- Potential **PREVENTIVE** therapy to avoid reinfection once a nail has been cleared
2. **TOPICAL TREATMENT FOR ONYCHOMYCOsis: IS IT MORE EFFECTIVE THAN THE CLINICAL DATA SUGGESTS?**


- “Complete Cure” is a strict, complicated number meant for clinical trials
  - Mycological cure + clinical cure
  - Clinical trials vs clinical practice reality: Great toenails vs lesser nails, time to treat in clinical trials vs real life

- Reviewed Phase III data for efinaconazole and tavaborole

- Clinical trial data vs efficacy seen in clinical practice
<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>EFINACONAZOLE</th>
<th>TAVABOROLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete cure</td>
<td>16.6%</td>
<td>6.5% and 9.1%</td>
</tr>
<tr>
<td>Clear nail (0% affected target toenail) unrelated to mycologic cure</td>
<td>19.7%</td>
<td></td>
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<tr>
<td>Complete or almost complete cure (≤5% affected toenail) and mycologic cure</td>
<td>25.0%</td>
<td></td>
</tr>
<tr>
<td>Completely or almost clear nail (≤5% affected toenail) and negative culture</td>
<td>31.8%</td>
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</tr>
<tr>
<td>Completely or almost clear nail (≤5% affected toenail) unrelated to mycologic cure</td>
<td>32.2%</td>
<td></td>
</tr>
<tr>
<td>Completely or almost clear nail (≤10% affected toenail) and negative mycology</td>
<td>15.3% and 17.9%</td>
<td></td>
</tr>
<tr>
<td>Completely or almost clear nail (≤10% affected toenail) and negative culture</td>
<td>24.6% and 25.3%</td>
<td></td>
</tr>
<tr>
<td>Completely or almost clear nail (≤10% affected toenail) unrelated to mycologic cure</td>
<td>26.1% and 27.5%</td>
<td></td>
</tr>
<tr>
<td>Treatment success (≤10% affected toenail) and mycologic cure</td>
<td>31.6%</td>
<td></td>
</tr>
<tr>
<td>Treatment success (≤10% affected toenail) unrelated to mycologic cure</td>
<td>42.6%</td>
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</table>
3. LONG-TERM FOLLOW-UP OF ONYCHOMYCOSIS PATIENTS TREATED WITH EFINACONAZOLE

- *J Drugs Dermatol. 2017 Dec 1;16(12):1269-1273*
- Single center, open label study; 22 subjects who were 18-80 with 40-75% clinical involvement
- QD application for 48 weeks, then two follow ups visits at weeks 60 and 72
- Complete cure, mycological cure, treatment success
- Nails take 52 to 78 weeks to grow out (or longer)
MYCOLOGICAL CURE

**Figure 1.** Mycologic cure* at end of treatment (week 48, N=23) and post-treatment follow-up (week 72, N=22). *defined as those subjects with both negative KOH examination and fungal culture.

- KOH + Culture
- Culture positive
- KOH positive
- Mycological cure

*J Drugs Dermatol. 2017 Dec 1;16(12):1269-1273*
4. IN VITRO EFFICACY OF TAVABOROLE TOPICAL SOLUTION, 5% AFTER PENETRATION THROUGH NAIL POLISH ON EX VIVO HUMAN FINGERNAILS

- *J Dermatolog Treat. 2018 Jan 10:1-4*

- Previous *ex vivo* studies showed tavaborole could inhibit *T. rubrum* and penetrate through a polished fingernail

- Is there fungicidal activity in the presence of nail polish?

- 4 coats of polish vs 2 coats vs unpolished
5. **ULTRASOUND-ENHANCED** DRUG DELIVERY FOR TREATMENT OF ONYCHOMYCOSIS

- *J Ultrasound Med. 2017 Dec 30*
- Increase permeability of the nail, enhance drug delivery
- 2 distinct sets of experiments with porcine nails:
  - Luminosity
  - Changes in nail permeability following US
- 1 Safety Modeling experiment showing thermal safety of US application with human toenail
TEMP SAFETY MODELING RESULTS

![Graph showing temperature increase over time for different tissues: Bone, Subq tissue, Nail bed, Nail, Skin.](image-url)
6. 1340NM LASER THERAPY FOR ONYCHOMYCOSIS: NEGATIVE RESULTS OF PROSPECTIVE TREATMENT OF 72 TOENAILS AND A LITERATURE REVIEW


• Monotherapy of the 1340 nm Nd:YAP laser with fluence of 22-25 J/cm²

• 72 toenails in 30 patients; mycological cure and patient satisfaction

• Follow up 12 weeks after 3 applications (1 session q 3 weeks)
<table>
<thead>
<tr>
<th>Patients/Nail Plates</th>
<th>Laser</th>
<th>Follow Up</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 patients (3 children)</td>
<td>1064nm Nd:YAG laser Q-switched (600mJ/cm²) 1 session</td>
<td>36 weeks</td>
<td>100% of clinical and mycological cure</td>
<td>Garcia, 2014</td>
</tr>
<tr>
<td>24 patients</td>
<td>3 sessions-30 days + amorolfine cream</td>
<td>24 weeks</td>
<td>50% of clinical and mycological cure</td>
<td>Lim et al, 2014</td>
</tr>
<tr>
<td>10 patients 10 controls with cryogen</td>
<td>1320nm Nd:YAG laser 4 sessions</td>
<td>12 weeks</td>
<td>45%—linear growth</td>
<td>Ortiz et al, 2014</td>
</tr>
<tr>
<td>37 patients, 112 plates 39 patients, 118 plates (itraconazole)</td>
<td>Nd:YAD long pulse</td>
<td>8, 16, and 24 weeks</td>
<td>Itraconazole greater efficacy with 8 and 16 weeks, but equal at 24 weeks</td>
<td>Li et al, 2014</td>
</tr>
<tr>
<td>24 patients</td>
<td>Diode 1064nm (5J/cm²/80ms) 2 to 3 sessions-60 days</td>
<td>12 weeks</td>
<td>6 patients—clinical and mycological cure OSI—40% improvement</td>
<td>Rener et al, 2015</td>
</tr>
<tr>
<td>30 patients</td>
<td>1064nm Nd:YAG laser short pulse</td>
<td>48 weeks</td>
<td>20 patients—clinical and mycological cure</td>
<td>Helou et al, 2016</td>
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7. RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF COMBINATION THERAPY WITH SHORT-PULSED 1,064-NM NEODYMIUM-DOPED YTTRIUM ALUMINIUM GARNET LASER AND AMOROLFINE NAIL LACQUER FOR ONYCHOMYCOSIS


- 64 patients in Nd:YAG + Amorolfine group; 64 patients in amorolfine monotherapy

- Laser applied once every four weeks (4 sessions total) with amorolfine applied once weekly for 16 weeks; fluence of laser 200 mJ/cm²

- “cure rate” in combo group: 71.88% vs topical monotherapy: 20.31%
### SIXTEEN WEEKS CUMULATIVE CURE RATE

<table>
<thead>
<tr>
<th>Cumulative cure rate</th>
<th>Case (n=64)</th>
<th>Control (n=64)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not cured</td>
<td>18 (28.1)</td>
<td>51 (79.7)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Complete remission</td>
<td>46 (71.9)</td>
<td>13 (20.3)</td>
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ORAL ANTIFUNGAL SAFETY

• Am J Med. 2007;120:791-798 (B)
• Meta-analysis of 122 studies with 20,000 patients
• Pooled risks of treatment discontinuation from AEs:
  • 3.4% for terbinafine 250 mg/d
  • 4.21% for itraconazole 200 mg/d
• Risk of liver injury requiring termination of treatment:
  • Less than 2.0% for all regimens
• Risk of having asymptomatic elevation of LFTs:
  • Less than 2.0% for all regimens
• Bottom line: well tolerated and safe in an immunocompetent population
8. RISK OF PSORIASIS FOLLOWING TERBINAFINE OR ITRACONAZOLE TREATMENT FOR ONYCHOMYCOSIS: A POPULATION-BASED CASE-CONTROL COMPARATIVE STUDY

- *Drug Saf. 2017 Nov 6*

- Several case studies suggesting link between oral antifungal and psoriasis

- 3800 + cases of psoriasis reviewed

- Both medications caused a risk of developing psoriasis
  - 1.33, 95% CI

- More recent exposure increased risk
  - 2.96, 95% CI less than or equal 90 day window

- Itraconazole monotherapy higher risk than terbinafine monotherapy
  - 1.21, 95% CI
• Dermoscopy characteristics can assist in clinical diagnosis of DLSO
• The topicals would likely benefit from more than 48 weeks use, and in ex vivo studies seem to have antifungal activity in the presence of nail polish
• No consensus on the efficacy of lasers for toenails
  • No standardization and lack of evidence showing it effective as monotherapy
• We need standardization to define “cure” i.e. clinical trials vs clinical practice
• More research needed for the oral antifungal/psoriasis risk
DON'T THINK YOUR TOE NAILS ARE NOT GROWING

I CUT THEM WHEN YOU SLEEP

THANK YOU!!!

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