Client: HMSA: PQSR 2009

Measure Title: HEPATIC ENZYME MONITORING FOR PERSONS USING ANTIMYCOTIC PHARMACOTHERAPY (TERBINAFINE AND ITRACONAZOLE)

Disease State: Liver Disease

Indicator Classification: Medication Monitoring

Strength of Recommendation: B

Organizations Providing Recommendation: American Academy of Family Physicians

Clinical Intent: To ensure that all eligible members who have a new prescription for certain antimycotic pharmacotherapy receive the necessary pretreatment evaluation.

Physician Specialties (suggested): Refer to PQSR 2009 Clinical Measures by Specialty.

Background: Disease Burden

- Estimates for the prevalence of onychomycosis in North American Countries range from 8-14%. [1-3] However, other cross-sectional studies show that this rate may vary by age and occupation. [4, 5]
- Risk factors for onychomycosis include exposure to family members with the disease, immunodeficiency, diabetes, psoriasis, tinea pedis, frequent swimming, and older age. [6]
- Generally, affected nails are visibly abnormal, causing embarrassment and negative effects on patients’ personal, social and occupational functioning. [7-9]

Reason for Indicated Intervention or Treatment

- When compared to older antifungal medications griseofulvin, terbinafine and itraconazole have higher cure rates in randomized controlled trials. [10-12]
- While fluconazole is also found to be effective in patients with onychomycosis, it is not as effective in terms of cost or cure as itraconazole and terbinafine. [13]

Evidence Supporting Intervention or Treatment

- Terbinafine’s hepatotoxic effects are acknowledged in the drug’s product monographs, [14] and have been reported multiple times in the literature, [15-28] and Itraconazole-induced hepatotoxicity has also been well-documented. [29-34]
- The FDA has issued a public health advisory about terbinafine and itraconazole citing the association between congestive heart...
failure and hepatic adverse events with the administration of these therapies.[35]

- There are at least 16 case reports in the English literature describing the development of necro-inflammatory and cholestatic hepatotoxicity with terbinafine use [15-27], and at least 5 case reports from non-English literature.[28, 36-39] Similarly, multiple case reports have described hepatotoxicity associated with itraconazole use.[29, 30, 32, 33]

- A 2007 meta analysis of 122 studies, involving a total of 19,298 patients reported that pooled risks (95% confidence intervals) of oral antifungal treatment discontinuation resulting from adverse reactions for continuous therapy were 3.44% (95% confidence interval [CI], 2.28%-4.61%) for terbinafine 250 mg/day; 1.96% (95% CI, 0.35%-3.57%) for itraconazole 100 mg/day; 4.21% (95% CI, 2.33%-6.09%) for itraconazole 200 mg/day; and 1.51% (95% CI, 0%-4.01%) for fluconazole 50 mg/day. For intermittent therapy, the pooled risks were as follows: pulse terbinafine: 2.09% (95% CI, 0%-4.42%); pulse itraconazole: 2.58% (95% CI, 1.15%-4.01%); intermittent fluconazole 150 mg/week: 1.98% (95% CI, 0.05%-3.92%); and intermittent fluconazole 300 to 450 mg/week: 5.76% (95% CI, 2.42%-9.10%).

- According to this meta-analysis, the risk of liver injury requiring termination of treatment ranged from 0.11% (continuous itraconazole 100 mg/day) to 1.22% (continuous fluconazole 50 mg/day). The risk of having asymptomatic elevation of serum transaminase but not requiring treatment discontinuation was less than 2.0% for all treatment regimens evaluated.[40]

- The crude incidence rate of acute liver injury associated with itraconazole use is approximately 1:10,000.[31]

- A cohort study of 19,488 patients showed that patients taking itraconazole had a relative risk of 17.7 (95% confidence interval 2.6, 72.6) of developing acute liver injury when compared to the risk among nonusers.[31]

**Clinical Recommendations**

- For continuous treatment, the American Academy of Family Physicians recommends checking baseline liver enzyme levels before starting terbinafine or itraconazole, and then testing every four to six weeks during treatment. No testing is suggested for pulse therapy.[41]

**Source**

Health Benchmarks, Inc.

**Denominator**

| Denominator Definition | Continuously enrolled members who filled at least 1 prescription for oral treatment with Lamisil (terbinafine) or Sporanox (itraconazole) during the first 358 days of the measurement year. |
### Denominator Exclusion

**Denominator Definition**
Members who filled a prescription for oral treatment with Lamisil (terbinafine) or Sporanox (itraconazole) during the 1-365 days prior to the index date.

### Numerator

**Numerator Definition**
Members who have had appropriate monitoring lab work (i.e. hepatic function panel, general health panel, AST, ALT) completed during the 90 days prior through 7 days after the index date.

### Physician Attribution

**Physician Attribution Description**
Score only the physician who prescribed the member Lamisil (terbinafine) or Sporanox (itraconazole) on the index date (i.e. denominator criterion A).

### References


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