Pharmacoeconomic analysis of ciclopirox nail lacquer solution 8% and the new oral antifungal agents used to treat dermatophyte toe onychomycosis in the United States

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of ciclopirox 8% (continuous therapy), a novel topical lacquer, for the treatment of onychomycosis of the toe.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study populations comprised patients with toenail onychomycosis.

Setting
The setting of the study was unclear, but it appears to have been that of secondary care. The economic study was carried out in Toronto (ON), Canada.

Dates to which data relate
The effectiveness and resource use data were gathered from studies published between 1990 and 2000. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a systematic review of published studies.

Modelling
A decision analytic model (decision tree) was constructed for the treatment of dermatophyte onychomycosis of the toes. This reflected the current practice for treating the disease in the USA, after the initial introduction of a topical nail lacquer. Each of the therapies was considered as first-line therapy. The time horizon of the study was 3 years. The outcomes (mycologic cure, cure followed by relapse, or failure) were assessed after 1 year. Those patients who had relapsed or failed after initial therapy had an equal probability of receiving terbinafine,itraconazole (pulse), or ciclopirox nail lacquer.

Outcomes assessed in the review
The main outcome measure assessed in the review was the mycologic cure rate. This was defined as a negative light microscopic examination and a negative culture. The clinical response rate and the relapse rate were also obtained from the literature. The clinical response was a clinical evaluation, which combined clinical cure and marked improvement.
Study designs and other criteria for inclusion in the review
The study designs obtained from the review of the literature were all prospective, and mainly blinded and randomised. For inclusion in the review, the studies had to meet the following criteria:

- the entry criteria for the trial were based on the clinical and mycologic diagnosis of onychomycosis;
- the etiologic agent of the disease distinguished between dermatophytes and nondermatophytes;
- the duration of the study was more than 6 months for griseofulvin and ciclopirox nail lacquer, and at least 3 months for itraconazole, terbinafine and fluconazole;
- the dosage was 500 mg/day for griseofulvin,
- the dosage for itraconazole was 200 mg/day (continuous), or 200 mg twice daily for 1 week each month, with successive pulses at 1-month intervals (pulse);
- the dosage was 250 mg/day for terbinafine;
- the dosage was 150 mg once weekly for fluconazole;
- ciclopirox nail lacquer was applied at a frequency varying from once weekly to once daily;
- the end points of the therapy and the efficacy measures were clearly stated;
- the site of infection was mentioned;
- there was a minimum sample of 50 immunocompetent patients;
- the efficacy rates were reported at 12 months from the start of the therapy; and
- the relapse rates were reported at 12 to 18 months from the start of the therapy.

Sources searched to identify primary studies
The databases MEDLINE and EMBASE were searched from 1996 to 1999 for publications in the English language. The reference sections of the retrieved articles were then used as a further source of data on the efficacy of the therapies.

Criteria used to ensure the validity of primary studies
It was preferable for the studies to be blinded.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The effectiveness evidence were derived from 41 studies.

Methods of combining primary studies
The data were combined using a meta-analysis. This resulted in a average for each efficacy rate, weighted by sample size, pertaining to the different drug comparators. The 95% confidence intervals (CIs) were also calculated.
Investigation of differences between primary studies
Not reported.

Results of the review
The average mycologic cure rate (+/- the standard error) from the meta-analysis was:

41.1% (+/- 20.4; 95% CI: 1.2 - 81.0) for griseofulvin;
66.3% (+/- 4.2; 95% CI: 58.1 - 74.6) for itraconazole (continuous);
70.8% (+/- 5.7; 95% CI: 59.6 - 82.1) for itraconazole (pulse);
77.2% (+/- 4.0; 95% CI: 69.3 - 85.1) for terbinafine;
65.6% (+/- 7.1; 95% CI: 51.7 - 79.5) for fluconazole; and
52.6% (+/- 4.2; 95% CI: 44.6 - 60.7) for ciclopirox nail lacquer.

The average clinical response rate (+/- the standard error) from the meta-analysis was:

33.7% (+/- 14.1; 95% CI: 6.1 - 61.4) for griseofulvin;
70.3% (+/- 4.2; 95% CI: 62.1 - 78.5) for itraconazole (continuous);
73.6% (+/- 4.6; 95% CI: 64.6 - 82.7) for itraconazole (pulse);
75.3% (+/- 2.9; 95% CI: 69.6 - 81.0) for terbinafine;
66.5% (+/- 11.7; 95% CI: 43.6 - 89.5) for fluconazole; and
52.4% (+/- 9.0; 95% CI: 34.8 - 70.0) for ciclopirox nail lacquer.

The relapse rates, which were not obtained from the meta-analysis, were 40% for griseofulvin, 21% for itraconazole (continuous), 10.4% for itraconazole (pulse), 15% for terbinafine, 4.4% for fluconazole, and 20.7% for ciclopirox nail lacquer.

Measure of benefits used in the economic analysis
The benefit measures used in the economic analysis were the mycologic cure rate and the expected number of symptom-free days (SFDs). These were derived from the decision model for each drug therapy. The latter measure (SFDs) was obtained after determining the time taken to achieve mycologic cure.

Direct costs
Discounting was not carried out, although it would appear to have been relevant because the time horizon of the analysis was 3 years. The quantities of the resources used were reported separately from the unit costs. The cost/resource boundary was consistent with the perspective adopted. The cost analysis included the costs for drug acquisition, medical treatment, and the treatment of adverse events. The medical treatment costs covered consultation, return visits, the mycologic examination, and laboratory testing such as liver function test and complete blood count.

The costs were estimated from actual data ("Drug topics red book pharmacy's fundamental reference" and "Health Care Finance Administration"). The resources were mainly estimated from information and guidelines contained in the package inserts for the drugs, and from the standard practice views of a panel of physicians who had special interest and knowledge of the disease field. The data relating to the resources used were gathered from studies published from 1990 to 2000. The price year was not reported.
Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were conducted to assess the effect on “cost-effectiveness” when the clinical response rate was also used as the main outcome measure. The type of analysis conducted was not reported.

Estimated benefits used in the economic analysis
The mycologic cure rate was 0.411 for griseofulvin, 0.663 for itraconazole (continuous), 0.708 for itraconazole (pulse), 0.772 for terbinafine, 0.656 for fluconazole, and 0.526 for ciclopirox nail lacquer.

The expected number of SFDs was 415 for griseofulvin, 554 for itraconazole (continuous), 612 for itraconazole (pulse), 612 for terbinafine, 620 for fluconazole, and 563 for ciclopirox nail lacquer.

Cost results
The cost of the drugs was $1,015.2 for griseofulvin, $1,187.8 for itraconazole (continuous), $593.9 for itraconazole (pulse), $642.6 for terbinafine, $599.6 for fluconazole, and $149.9 for ciclopirox nail lacquer.

The cost of medical treatment was $396 for griseofulvin, $215 for itraconazole (continuous), $215 for itraconazole (pulse), $245 for terbinafine, $366 for fluconazole, and $173 for ciclopirox nail lacquer.

The cost of treating adverse effects was $1.9 for griseofulvin, $7.4 for itraconazole (continuous), $2.8 for itraconazole (pulse), $2.5 for terbinafine, $1.2 for fluconazole, and $0 for ciclopirox nail lacquer.

The total cost of the regimen was $1,413.1 for griseofulvin, $1,410.2 for itraconazole (continuous), $811.7 for itraconazole (pulse), $890.1 for terbinafine, $966.8 for fluconazole, and $352.2 for ciclopirox nail lacquer.

Synthesis of costs and benefits
The costs and benefits were combined using average and incremental cost-effectiveness analyses.

The average cost per mycologic cure was $3,438.2 for griseofulvin, $2,126.9 for itraconazole (continuous), $1,146.4 for itraconazole (pulse), $1,153 for terbinafine, $1,473.7 for fluconazole, and $618.2 for ciclopirox nail lacquer.

The average expected cost per patient was $2,198.5 for griseofulvin, $1,951.3 for itraconazole (continuous), $1,232.1 for itraconazole (pulse), $1,311.5 for terbinafine, $1,303 for fluconazole, and $953.6 for ciclopirox nail lacquer.

The average expected cost per expected SFD was $5.30 for griseofulvin, $3.52 for itraconazole (continuous), $2.01 for itraconazole (pulse), $2.14 for terbinafine, $2.10 for fluconazole, and $1.69 for ciclopirox nail lacquer.

The relative cost-effectiveness ratios were also calculated, with the drug comparator having the lowest expected cost per expected SFDs being assigned a value of 1. The relative ratios were 1 for ciclopirox nail lacquer, 1.19 for itraconazole (pulse), 1.24 for fluconazole, 1.27 for terbinafine, 2.08 for itraconazole (continuous), and 3.13 for griseofulvin.
The incremental cost-effectiveness ratio of ciclopirox nail lacquer was 5.68 over itraconazole (pulse), 6.14 over fluconazole, and 7.30 over terbinafine. Griseofulvin and itraconazole (continuous) were both dominated by ciclopirox.

In the sensitivity analysis, it was stated that ciclopirox nail lacquer remained the most cost-effective strategy when the clinical response rate was used as the primary efficacy parameter.

**Authors' conclusions**
Ciclopirox nail lacquer solution 8% was the most cost-effective strategy for the treatment of dermatophyte toe onychomycosis, when compared with oral antifungal agents commonly used in the USA.

**CRD COMMENTARY - Selection of comparators**
The authors justified their selection of the comparators on the grounds that they represented drug therapies used to treat the disease in the USA, before the introduction of ciclopirox nail lacquer. You should consider whether they represent widely used technologies in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was derived from a meta-analysis of published literature on the treatment of onychomycosis. The methods and conduct of the review appear to have been sound and were reported satisfactorily. Numerous inclusion criteria were used to select reliable primary studies. The method used to combine the studies was indicated clearly.

**Validity of estimate of measure of benefit**
The benefit measures were derived from a decision model. This was appropriate since it reflected the treatment of the disease in the USA. Unfortunately, the measure of benefit was particular to this condition, and it did not allow a comparison with other technologies in terms of the quality of life or preferences.

**Validity of estimate of costs**
The estimation of the costs appeared to be quite specific to the study setting, i.e. the DRG reimbursement system. The perspective of the study was not reported, but it appears to have been that of the third-party payer, which is reimbursed according to the DRG system. The quantities of the resources used and the unit costs were reported separately, thus enhancing the external validity of the study. However, sensitivity analyses were not carried out on the cost elements. In addition, the price year was not reported.

The cost-effectiveness depends on the incremental cost per incremental health benefit, in comparison with the next most expensive technology. Unfortunately, this was not recorded accurately in the paper. Itraconazole (continuous) was stated to be dominated by ciclopirox, but it had a higher cure rate. In fact itraconazole should have been compared with fluconazole because this was the next most expensive treatment, although it would still have been dominated. Terbinafine would also have been dominated if using SFDs. This leaves itraconazole (pulse) and fluconazole. Itraconazole (pulse), when compared with ciclopirox, gave an incremental cost of $486.5 for a gain of 49 SFDs. Fluconazole, which was $76.7 more expensive than terbinafine, gave 8 more SFDs. Therefore, one would have to consider a sacrifice of SFDs in order to save money by adopting ciclopirox.

**Other issues**
The authors did not compare their findings with those from other studies, mainly because this was the first analysis examining the comparison of ciclopirox nail lacquer with oral agents in the USA. The generalisability of the study to other settings was limited because only a few sensitivity analyses were carried out on the effectiveness side of the analysis. One possible limitation of the study, as pointed out by the authors, was that the efficacy data for ciclopirox were derived from US trials enrolling patients with moderate or mild dermatophyte toe onychomycosis. Therefore, the analysis could be biased toward ciclopirox. However, trials conducted outside of the USA indicated that the drug could...
be effective also for more severe stages of the disease.

**Implications of the study**
The authors claimed that ciclopirox nail lacquer was cost-effective and free of serious adverse effects. In addition, ciclopirox could be especially beneficial for patients who are not good candidates for oral antifungal therapy, or as second-line treatment after the failure of other interventions. However, the evidence presented did not support the claim relating to the cost-effectiveness of ciclopirox. In fact, ciclopirox, although the cheapest technology studied, was not as effective as some other technologies. Therefore, a sacrifice would have to be made in the effectiveness if money were to be saved.

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