Pharmacoeconomics – an aid to better decision-making

R Arenas-Guzman,*† A Tosti,‡ R Hay,§ E Haneke¶
† Calz. De Tlalpan 4800, Col. Toriello Guerra, Mexico; ‡ University of Bologna, Via Castiglione 72, Bologna, Italy; § Faculty of Medicine and Health Sciences, Queen’s University Belfast, Whittan Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK; ¶ Schlippehof 5, D-79110 Freiburg i.Br., Germany.
* Corresponding author: Calz. De Tlalpan 4800, Col. Toriello Guerra, Mexico, D.F., C.P. 14310, tel. +525 56 65 76 91;
E-mail: rarenas@micologiamedica.org or rarenas98@hotmail.com

ABSTRACT
Objectives The first aim of this workshop was to define pharmacoeconomic concepts and terminology. Pharmacoeconomics can be defined as the branch of economics that uses cost-benefit, cost-effectiveness, cost-minimization, cost-of-illness and cost-utility analyses to compare pharmaceutical products and treatment strategies. Economic evaluations provide healthcare decision-makers with valuable information, allowing optimal allocation of limited resources. However, pharmacoeconomics is based on long-term benefits, whereas physicians are typically forced to seek immediate savings. The second aim was to review pharmacoeconomic studies in the field of onychomycosis and finally to discuss future perspectives.

Results and Conclusions We discussed current pharmacoeconomic issues on the management of onychomycosis. Consensus was reached on the following issues:
• Published pharmacoeconomic studies concerning onychomycosis are flawed. Future studies should be based on internationally validated principles and appropriate models. The fact that costs of different drugs, laboratory examinations and physician visits vary worldwide should be considered. Cost-benefit studies are required.
• The National Institute for Clinical Excellence (NICE) recommendations are often considered in countries other than the UK, even when not adapted to the country in question.
• Generic drugs might reduce costs, but this depends on their effectiveness (bioavailability).
• Sampling requests affect the economic cost (dependent on methodology, which depends on country) and physicians often trust their instincts even when tests are repeatedly negative.
• The cost of adverse event management is usually considered to be 10%; this may be too high for onychomycosis, as treatments are relatively safe without severe side-effects.
• Probability of recurrence for each drug should be determined.
• Need for disease severity standardization, definition of diagnostic criteria and successful treatment (mycological and clinical cure).

Key words: cost-effectiveness studies, drugs, onychomycosis, pharmacoeconomics

What is pharmacoeconomics?
Definitions
The key aim of all economic analyses is to make the best choice within defined parameters. Pharmacoeconomics is the branch of economics related to the most economical and efficient use of pharmaceuticals; economic approaches are applied to pharmaceuticals to guide the use of limited resources to yield maximum value to patients, health care payers and society in general.

Cost-effectiveness studies are of utmost importance to justify expenditure in all fields of health care (fig. 1). However, the term ‘cost-effective’ is often used incorrectly. In fact, there are several types of pharmacoeconomic evaluation,1 each of which is useful in different circumstances:
Cost-of-illness analyses consider the costs of a given disease without considering the outcome.

Cost-minimization analyses compare the costs of interventions that provide the same outcome, with the ultimate aim of identifying the cheapest option.

Cost-effectiveness analyses involve the comparison of cost per standardized unit of effectiveness for two or more interventions that provide varying outcomes.

Cost-utility analyses aim to compare the cost per quality-adjusted life-year for two or more interventions that provide varying outcomes.

Finally, cost-benefit analyses compare the costs and benefits of two or more interventions that provide varying outcomes, where outcome is measured in monetary terms.

Key components
The main components that must be considered in any pharmacoeconomic evaluation are (fig. 1):

- perspective (health trust, governmental body, insurance company, patients, society in general);
- time horizon;
- cost (direct medical costs, direct nonmedical costs, indirect costs, intangible costs); and
- outcome (years of life saved, years of disease-free survival, cure rate).

Outcome
It is generally considered that there are four principal outcomes of pharmacoeconomic studies:

(i) Lower cost, better outcome
(ii) Higher cost, better outcome
(iii) Lower cost, poorer outcome
(iv) Higher cost, poorer outcome

It is of course conceivable that a given drug could cost more or less than its competitor while resulting in the same outcome. Clearly, the first outcome is the most favourable for the use of the new treatment. Conversely, the last outcome does not favour the use of the new drug.

When the second or third outcome arises, the choice of treatment is up to the prescribing doctor, prescribing policy and the budget available. In such situations, it is also necessary to look at other differences between agents that may sway the decision to prescribe one drug rather than another. These differences may include pharmacokinetic and pharmacodynamic traits, the risk of drug interactions and compliance rates.

Pharmacoeconomics and onychomycosis
The treatment of onychomycosis is costly. It has been estimated that the direct cost of treating onychomycosis for US Medicare patients is $43 million per year.2 Until recently, relatively few agents were available for the treatment of onychomycosis. The availability of new drugs means that physicians now have a wide choice of possible treatment strategies. Furthermore, newer generation drugs are generally more expensive than older generation drugs. Given the increasing prevalence of fungal nail infections and the associated costs and burden to the healthcare systems, it is important to select the most cost-effective treatments. Therefore, several pharmacoeconomic studies have been carried out to compare the relative cost-effectiveness of various treatment options to aid healthcare providers and patients in deciding which agent to use.

Cost-effectiveness of diagnosis
It is common practice to initiate treatment before confirming the diagnosis of onychomycosis. Only one study has evaluated the cost-effectiveness of diagnosis.3 This study compared the cost-effectiveness of initiating treatment after diagnostic testing vs. initiating treatment without diagnostic testing in 688 patients. They found that pretreatment diagnostic testing led to a saving of $159 per patient. Furthermore, confirming diagnosis before treating avoids unnecessary exposure to antifungals and thus reduces the risk of adverse effects.

General retrospective pharmacoeconomic studies
Humphrey et al. performed a retrospective analysis to compare the cost-effectiveness of terbinafine, tioconazole, amorolfin and griseofulvin.4 By calculating direct treatment costs (drugs, medical consultations, minor surgery, etc.) and mycological and clinical cure rates (based on the results of a previous multinational study), they found that terbinafine was the most cost-effective option.4 However this study also presented a flaw leading to an incorrect conclusion. When estimating the efficacy
of amorolfine, the authors stated that 110 days of amorolfine applications corresponded to 3.7 months of treatment, which is not true. In practice, amorolfine is used once or twice per week so this number of applications corresponds to between 1 and 2 years of treatment. Therefore, at least for the cost-effectiveness analysis, they should have used the published cure rate (around 55%). If we repeat the cost-effectiveness analysis with this cure rate, we see that amorolfine is the most cost-effective therapy.

**Review of pharmacoeconomic analyses**

**Oral treatments**

Arikian *et al.* conducted a multinational cost-effectiveness analysis comparing four oral treatments (griseofulvin, itraconazole, ketoconazole and terbinafine) in 13 countries from a healthcare system perspective. They developed a four-step pharmacoeconomic research model including factors affecting costs:

(i) Problem identification, drug dosage, drug identification and type of patient

(ii) Clinical management. The healthcare resources used during treatment and the management of adverse effects were established: three clinical outcomes were determined (clinical success rate, relapse rate and adverse effect rate)

(iii) Economic analysis (drug acquisition costs, drug administration costs, routine medical care, laboratory test costs and costs associated with management of adverse drug reactions)

(iv) Sensitivity analysis.

This model demonstrated that terbinafine was the most cost-effective oral treatment in terms of disease-free days. Obviously, this study simply assessed oral treatments in isolation without considering topical treatments alone or combined topical and oral treatments.

This model has since been implemented in other clinical studies aiming to identify the most cost-effective oral antifungal for use in monotherapy. For example, Einarson *et al.*, Marchetti *et al.*, Van Doorslaer *et al.*, Gupta and Bootman used a similar model to compare oral monotherapies; all found that terbinafine was the most cost-effective, regardless of the perspective (healthcare payer, third-party payer, government payer). Once again, topical treatments were not assessed singly or in combination with orals.

Angello *et al.* showed that the cost per mycological cure was $388 for terbinafine (pulse), $648 for terbinafine (continuous), $855 for itraconazole (pulse), $1845 for itraconazole and $2721 for griseofulvin. Interestingly, this demonstrates that pulse therapy is more cost-effective than continuous therapy in the USA.

Jansen and coworkers compared two newer generation oral drugs (terbinafine and itraconazole) in six European countries. Cost-effectiveness analysis showed that terbinafine was the preferred strategy in five of the six countries (Germany, Iceland, Italy, the Netherlands and UK). However, the most cost-effective drug was itraconazole in Finland. This study demonstrates that costs and prescribing practices vary from country to country, a point that has rarely been considered.

Most of these studies took into account the costs of the drug, the management of adverse reactions, medical management and clinical efficacy, but did not consider drug interactions or compliance (always assumed to be 100%). Furthermore, none of these studies compared available oral and topical treatments. The findings of such studies would be interesting because side-effects and drug interactions are significantly more common with oral therapies than with topical therapies.

**Topical treatments**

Most prior studies compared only different types of oral monotherapy. Only one study has compared the cost-effectiveness of three types of topical monotherapy. Marty *et al.* assessed the weighted average cost per patient cured of treatment with three nail lacquers: amorolfine 5% nail lacquer, ciclopirox 8% nail lacquer and tioconazole 28% nail solution. Their analysis was based on the quantity of drug required (rounded up to whole bottles) based on recommended treatment regimens, the surface area and the number of infected nails, and the mycological cure rate. They found that amorolfine was the most cost-effective treatment for toenail, fingernail and mixed infections in both male and female patients: for example, the cost per cured patient in France (where tioconazole is not available) was €79.94 with amorolfine compared to €236.59 with ciclopirox. Analyses in Italy and UK showed that the cost of tioconazole per patient was even higher (~€475 and ~€675, respectively). Hence, in France, Italy and UK, amorolfine is a dominant strategy because it is more effective and less expensive than competitors.

**Combination therapy**

The vast majority of pharmacoeconomic studies have concerned only monotherapies (particularly oral monotherapy). However, in recent years, several groups have performed cost-effectiveness studies on combination therapies. These studies have shown that although combination therapy may initially appear to be an expensive option because two drugs are prescribed simultaneously, it is both cost-saving and cost-effective compared to oral treatment alone. This is because the oral drug can be prescribed for shorter periods when combined with a topical drug, which decreases the drug acquisition costs and the costs associated with adverse event management. The results of Angello’s study suggest that this advantage may be even greater when the oral component is given in pulse form.

In their pilot study of terbinafine alone and in combination with amorolfine 5% solution, Zaug and Bergratraesser found that combination therapy had a better cost per cure ratio than monotherapy.
A second, larger study, based only on drug acquisition costs, showed that the combination of amorolfine 5% nail lacquer with oral terbinafine for 12 weeks was more cost-effective (lower cost per cure ratio) than oral terbinafine alone for 6 weeks or the combination of amorolfine 5% nail lacquer with oral terbinafine for 12 weeks.

Lecha and colleagues carried out an open-label, multicentre study to compare the combination of amorolfine nail lacquer and oral itraconazole (for 6 or 12 weeks) vs. oral itraconazole alone for the treatment of severe toenail onychomycosis. This study included a simplified pharmacoeconomic analysis based only on the public price of each drug, the amount of each drug used and the overall cure rate at week 24. They did not consider costs related to treatment failure or tolerability monitoring (e.g., liver function tests). Likewise, the costs of treating adverse events were not considered because the number and nature of adverse events were similar in all groups. The conclusion of this preliminary study was that the combination of amorolfine for 24 weeks with itraconazole for 6 weeks was the most cost-effective option, especially compared to itraconazole monotherapy. It is possible that the cost-effectiveness of itraconazole monotherapy would have been even lower if treatment failure, tolerability monitoring and adverse events were considered.

Rigopoulos et al. carried out a simplified pharmacoeconomic analysis comparing itraconazole alone and in combination with amorolfine 5% nail lacquer for the treatment of Candida onychomycosis. This analysis, which was based uniquely on drug acquisition costs, demonstrated that combination therapy was more cost-effective than monotherapy. Combination therapy also had an itraconazole-sparing effect; this is advantageous because itraconazole is associated with a fairly high rate of adverse events, which are costly to manage and may have a negative effect on patient compliance and therefore success rates, further decreasing cost-effectiveness.

In conclusion, there is a clear need to compare available oral and topical treatments. Indeed, as mentioned above, the rate of side-effects and drug interactions is considerably lower with topical therapy than with oral therapy. The results of previous studies suggest that for severe onychomycosis, the most cost-effective treatment for onychomycosis is combination therapy with an oral drug (pulse) together with amorolfine. When oral drugs are given in combination with topical therapy, treatment period may be shorter. This lowers the risk of side-effects and hence, the cost of their management. The synergy between the two drugs increases the success rate and might improve patient compliance. Furthermore, combination treatment with amorolfine and two pulses of itraconazole is associated with more rapid and greater mycological cure, increased total cure rate, no increase in adverse events and lower cost per patient than itraconazole alone. When topical treatments are compared, amorolfine is the most cost effective.

**Consensus workshop**

Most of the early pharmacoeconomic studies in the field of dermatology were flawed; newer studies are generally of a higher standard. Older studies directly transposed clinical figures into comparisons without making any adjustments for what would really happen in practice. There is a need for studies conducted in standardized conditions, subject to internationally validated principles. An appropriate mathematical model, such as a Bayesian model, needs to be applied.

It is important to remember that drug costs vary across the world. Studies can be carried out in the country that puts the study drug to the biggest advantage, which means that results cannot be extrapolated to other countries.

The National Institute for Clinical Excellence (NICE) guidelines are often taken into account in countries other than Britain, even though they may not be relevant to this country. It is rarer for guidelines published in other countries to be considered, mainly because of the language barrier.

There is an increasing demand for pharmacoeconomic data. In UK for example, all costly treatments have to be approved by NICE. NICE is beginning to look at dermatology products to decide which are acceptable and which are not.

Regulatory and licensing bodies are often asked to see cost-benefit data, but no such studies are available in onychomycosis. NICE wants cost-utility data to determine what would happen to other diseases if a given treatment is reimbursed.

Often, pharmacoeconomics is based on long-term savings whereas most doctors are forced to make decisions based on immediate cost savings. There is increasing pressure on doctors to not prescribe drugs and to consider their annual budget. For example, in Germany, doctors are held responsible for the total costs of all prescriptions. If they exceed a certain limit per quarter (January–March, April–June, etc.), an audit will be performed, and ultimately, the doctor will end up paying for their patients’ treatment. This makes doctors reluctant to prescribe costly treatments. For example, a doctor would need to see 10–15 patients who do not require any prescriptions to compensate the extremely high cost of itraconazole, which is extremely unlikely to happen. This is not the case in other countries, such as France, where the number of prescriptions is particularly high.

The German guidelines recommend that doctors should first prescribe topical treatments, but since last year, topical drugs are no longer reimbursed. This means that patients request oral drugs—a request that doctors find hard to refuse. These oral treatments are more expensive, associated with interactions and adverse events and often not really needed. This is also the case in Italy where topical drugs are not reimbursed.

Drugs are not reimbursable in Brazil. Hence, general physicians (GPs) tend to prescribe fluconazole as a generic version if it is available. The availability of generics may influence prescribing habits, but there are doubts about their effectiveness. For
instance, a generic drug available in Colombia was found to have a bioavailability of just 3.5% compared to the original drug. This situation is likely to worsen as price is often the only criterion considered by governments and regulatory bodies.

As in Germany, topical treatments are not reimbursed in Italy. The outcome is that mild cases are often left untreated. These mild cases may then become moderate or severe meaning that oral treatment is required. Thus, it could be argued that it would be more cost-effective to treat at an early stage, especially as disease severity affects the success rate.

Adverse events and medical management (consultations, mycology, liver function and haematology tests) mainly with oral treatments need to be taken into account when performing pharmacoeconomic analyses. As expected, the cost of adverse event management is generally considered less than 10% of the total regimen cost, as most treatments are relatively safe with few serious adverse events. On the other hand, medical management represents a considerable part of total regimen costs (~30%). Drug costs represent around 70%.

Other factors that make it difficult to compare previous studies are differences in study design. For example, efficacy rates are higher in open studies than in randomized controlled trials.

It is also important to define severity and patient inclusion criteria. For example, success rates are considerably higher in studies with a small number of patients than in the majority of studies. The only logical explanation for this is that participants had mild onychomycosis. Likewise, cure rates often appear low in UK, this is probably because GPs treat mild cases and only severe cases are referred to specialists (patients cannot consult specialists without a referral from their GP in UK). It is important that the severity of the disease in the study population be specified, otherwise data that should not be pooled may be pooled in meta-analyses.

Other terms that need defining include: clinical cure, mycological cure and total cure.

Pharmacoeconomic data can be used to influence drug choice. It could be useful to apply such data before initiating treatment. For instance, doctors know that they have virtually no chance of curing some patients; therefore, it may help them to explain to the patient that there is no point treating them. Another example is the case of elderly subjects who are already being treated with numerous drugs. In such cases, the patient often chooses to leave the prescribed medication in the back of the cupboard

Consensus
- Often, pharmacoeconomics is based on long-term savings, doctors are forced to seek immediate savings.
- Older published pharmacoeconomic studies have several flaws.
- Need for standardized definitions, cost-benefit studies and calculation of recurrence rates.
- Need to take country- and disease-specific factors into account.

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