eton to normal.[1] Estrogens are currently the treatment of choice in preventing postmenopausal bone loss.[1] They have additional benefits on cardiovascular risk. Treatment should be started early in the menopause and continued for at least 5 years.

However, there is no consensus as to whether all women should be treated, or just those judged to be at highest risk of developing osteoporosis (e.g. natural or surgical menopause at <45 years of age). The use of calcitriol in the prevention of postmenopausal osteoporosis has not been investigated.

Of the various drugs used in the treatment of patients with established postmenopausal osteoporosis, there are few or no comparative data to assess relative efficacy. In addition, available data for some of these agents are equivocal. Adequate dietary calcium is important, and supplements may be necessary.

There are marked geographical differences in the use of the various drugs. In the US and the UK, the initial choice in a patient with established postmenopausal osteoporosis is an estrogen.[6,15] Bisphosphonates and calcitonin are the most commonly used alternatives. It is worth noting that calcitonin has considerably higher acquisition costs than the other agents (see *Differential Features* table). However, this drug may be particularly appropriate in the first 6 weeks after a fracture because of its additional analgesic properties.[6]

Results from the largest study of calcitriol, which showed that it prevented fractures, indicate that calcitriol should be evaluated further.

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Amorolfine: topical therapy for mild onychomycosis

IN BRIEF Amorolfine is a novel antifungal drug that has been formulated as a nail paint. This paint has shown promise as a topical therapy for onychomycosis.

Approximately one-half of patients with mild disease not involving the nail matrix and predominantly dermatophyte infections have achieved mycological and clinical cure in relatively small clinical trials conducted to date. Efficacy appears to be greater in finger- versus toenails. The drug has also produced some encouraging results as an adjuvant to oral griseofulvin.

When applied to the nails in a paint formulation, amorolfine has been well tolerated. Fewer than 2% of treated patients have experienced adverse events, and all of the reported adverse events have been mild and localised to the site of application.

The drug appears to be a suitable alternative to other topical agents for use in patients with mild disease. However, patients with more extensive disease, including nail matrix involvement, require systemic therapy.

Amorolfine† is a novel antifungal agent, structurally unrelated to other available antifungal drugs.[1] It is applied topically for the treatment of superficial fungal infections of the skin and nails.

Although the drug appears to be effective topically in patients with superficial fungal infections of the skin,[2-4] the lack of trials comparing amorolfine with the plethora of available agents hinders evaluation of its role in these indications.

Thus, this article will consider the use of amorolfine nail paint in fungal infections of the nail (onychomycosis), a condition in which topical therapy has hitherto been disappointing and in which the results of trials of amorolfine have been encouraging.[5]

Onychomycosis

Onychomycosis may be caused by a variety of organisms including dermatophytes (e.g. *Trichophyton rubrum*), yeasts (e.g. *Candida albicans*) and moulds (e.g. *Scopulariopsis brevicaulis*).[5] Of these, the dermatophytes are the most frequent causative organisms.[5]

Onychomycosis is characterised by discolouration of the nail, hyperkeratosis and separation of the nail from the nail bed (onycholysis). In addition, onychomycosis is often secondary to, or accompanied by, fungal infections of the skin or other nail disorders.

There are 4 main types of onychomycosis, as follows.[1]

1 *Distal and lateral subungual.* This is the commonest form, in which the infection starts at the distal edge or side of the nail and progresses proximally.

† Amorolfine is not available in Australia, Canada, The Netherlands, Spain or the US.

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2 *Superficial white.* An uncommon form mainly observed in toenails, in which white 'islands' of infection arise in the superficial layers of the nail plate and may be scraped off.
3 *Proximal subungual.* An uncommon form in which the infection progresses distally from the nail fold.
4 *Total dystrophic.* A severe form of onychomycosis that may arise from any of the preceding presentations, and involving total destruction of the nail plate.

It has been estimated that almost 3% of the UK population is affected by dermatophyte nail infections.[6]

Amorolfine

Amorolfine is a morpholine drug that, in common with other antifungal agents, inhibits the formation of ergosterol, which is a component of the fungal cell membrane.[1] However, amorolfine inhibits enzymes at a later stage in the conversion of acetyl-coenzyme A to ergosterol than the azole or allylamine antifungals.

Amorolfine has *in vitro* activity against a wide range of fungi, with dermatophytes and dimorphic fungi being the most susceptible.[1]

In vivo evaluations suggest that the drug is inactive in systemic fungal infections, possibly because of rapid metabolism, extensive protein binding or reduced activity at core body temperatures.[1] However, animal studies have demonstrated that the drug is active in cutaneous *Trichophyton mentagrophytes* infections and vaginal candidiasis.[1]

Pharmacokinetics

The permeation of amorolfine into human nail appears to vary according to:

- nail layer (with more drug being present in the uppermost layers)
- disease (soft, diseased nails are less retentive than healthy, hard, compact nails)
- vehicle (penetration is better with the commercially available methylene chloride base than with ethanol, but worse than with penetration enhancers).[1]

However, it appears from *in vitro* permeation studies that amorolfine attains sufficient concentrations in both the nail plate and bed to have fungistatic and fungicidal activity against fungal species including dermatophytes and dimorphic fungi.[1]

Clinical trials

There do not appear to have been any placebo-controlled trials of amorolfine nail paint in the treatment of onychomycosis.

Trials involving a total of >600 patients have evaluated the efficacy and safety of 2 amorolfine nail paint concentrations (5 *vs* 2%) and dosage intervals (once *vs* twice weekly).[8,9] In these trials, patients had mild nail disease (affecting ≤80% of the nail surface with intact lunula and matrix), predominantly distal subungual infections affecting the toenails (>73% of patients) and generally caused by dermatophytes (*T. rubrum* in 51 to 59% of patients and *T. mentagrophytes* in 15 to 22%). Concomitant skin infections were treated with amorolfine 0.5% cream. Treatment for onychomycosis was continued until complete cure or for a maximum of 6 months.

Application of 5% nail paint was associated with significantly higher overall cure rates than 2% nail paint (38 *vs* 12%, respectively) when each was applied once weekly.[8]

Adis Evaluation

Key points in the overall evaluation of topical amorolfine in patients with onychomycosis

CLINICAL BENEFITS

- Appears to be more effective than alternative topical therapies
- Well tolerated
- Requires less frequent application than other topical agents

POTENTIAL LIMITATIONS

- Suitable only for mild disease without nail matrix involvement
- Therapy must be continued for 6 to 12 months without interruption

There was no statistically significant difference in cure rates when amorolfine 5% nail paint was applied once weekly or twice weekly (clinical and mycological cure was reported in 46 and 52% of patients, respectively).[9]

Both prolonged duration of treatment and relatively short duration of onychomycosis appear to increase the likelihood of clinical and mycological cure with amorolfine therapy.[1]

In addition, amorolfine appeared to be more effective in patients with *T. mentagrophytes* infection than *T. rubrum* infection.[8,9] The drug also appears to have greater efficacy in fingernail infections than in toenail infections.[1]

Amorolfine was well tolerated in both of these dose-finding trials. Mild, localised adverse effects were reported by ≤2% of patients and did not require drug discontinuation.[8,9]

There has been one nonblinded trial evaluating the use of amorolfine 5% nail paint as an adjuvant to twice-weekly oral therapy with griseofulvin.[10] One group of patients received amorolfine and griseofulvin 1 g/day for 2 months followed by amorolfine alone for 4 months. The other group received griseofulvin 1 g/day for 2 months then 0.5 g/day for a further 4 months. Patients receiving amorolfine had higher mycological cure rates than those receiving griseofulvin monotherapy at both 2 (42 *vs* 13%) and 6 months (67 *vs* 45%).[10]

While this study indicates that amorolfine may have an adjuvant role in patients requiring systemic therapy, the results require confirmation in a more rigorously designed study. Future studies would preferably include other comparators, such as combined therapy for 6 months and amorolfine monotherapy. In addition, it remains to be seen whether amorolfine would be a useful adjuvant to systemic therapy with more recently introduced antifungal agents.

Other drugs used in onychomycosis

Topical therapy plays a minor role in the therapy of onychomycosis. Systemic therapy is appropriate for the majority of patients with onychomycosis, particularly when infection extends proximally to the posterior nail fold.[5,7]

The benefits and limitations of some orally administered drugs used in the treatment of onychomycosis are summarised in table 1. Although there is a lack of comparative trials of these agents, itraconazole and terbinafine appear to be preferable to

Table 1. Comparison of the efficacy, benefits and limitations of orally administered antifungal agents used in the treatment of onychomycosis[5,7,11]

Feature	Griseofulvin	Ketoconazole	Itraconazole	Terbinafine
Cure rates (%)				
Toenails	10-50	50	73-79	80-85
Fingernails	≈80	≈80	64	71
Benefits	Well tolerated	Broad spectrum of antifungal activity	Well tolerated Broad spectrum of antifungal activity Persists in nails for long periods; short treatment courses (3 months) appear effective	Well tolerated Fungicidal *in vitro* at low concentrations Short treatment courses (3-6 months for toenails; 6 weeks for fingernails) appear effective
Limitations	Only active in dermatophyte infections Prolonged treatment required (4-6 months for fingernails; 12-15 months for toenails) Interacts with other drugs[a]	May cause hepatitis Prolonged treatment required (4-6 months for fingernails; 12-15 months for toenails) Interacts with other drugs[a]	Interacts with other drugs[a]	*In vivo* activity limited to dermatophytes May cause reversible cholestasis (1 in 40 000 patients) Interacts with other drugs[a]

a Predominantly those metabolised by the hepatic cytochrome P450 enzymes, such as anticoagulants and phenobarbital (phenobarbitone).

the older agents since they have produced higher cure rates, are not associated with a significant risk of hepatitis, and may be effective with shorter treatment courses.

There are few topical alternatives to amorolfine. Tioconazole† nail paint is commercially available in the UK, and is compared with amorolfine in the *Differential Features* table.

Although the 2 have not been directly compared, tioconazole appears to be less effective than amorolfine, and requires more frequent administration.

In another trial, a paste of bifonazole† 1% and urea 40% applied daily under occlusion was associated with a mycological and clinical remission rate of 46% at 24 weeks.[12] However, this approach appears to be less convenient and no more effective for patients than amorolfine nail paint.

Differential Features

Comparison of the features of amorolfine 5% and tioconazole 28% nail paints[1,13,14]

Feature	Amorolfine 5%	Tioconazole 28%
Drug class	Morpholine derivative	Imidazole
Mechanism of action	Inhibition of ergosterol biosynthesis ($\Delta^7\Delta^8$-isomerase and Δ^{14}-reductase)	Inhibition of ergosterol biosynthesis (C-14 demethylase)
In vitro activity		
Dematophytes	✓	✓
Pathogenic yeasts	✓/×	✓
Mycological and clinical cure rate in onychomycosis	38-55%	≤22%
Frequency of application	Once or twice weekly	Twice daily
Acquisition cost In the UK (£)	34.38 (5ml)	27.38 (12ml)

Symbols: ✓ = drug is generally active; ✓/× = drug has variable activity.

Prescribing and formulary considerations

The data relating to the efficacy of amorolfine in patients with onychomycosis may be considered to be preliminary. There appear to have been no published trials employing a treatment duration of >6 months, even though 9 to 12 months is the recommended duration of treatment for toenail disease.[13] Follow-up periods after treatment cessation have also been short (3 months), which confounds any conclusions regarding the risk of relapse following initial therapy.

In addition, amorolfine monotherapy has not been compared with either placebo or alternative antifungal therapies to date.

Trials of amorolfine monotherapy have been limited to patients with mild nail plate disease and no matrix involvement.[8,9] Thus, the drug may be useful in clinical practice for patients with similarly mild disease. For these patients, available data suggest that amorolfine 5% nail paint may be preferable to tioconazole 28% nail paint (see *Differential Features* table).

Nonetheless, the majority of patients will continue to require systemic therapy.[5,7]

While preliminary data suggest that amorolfine may be a useful adjuvant to oral griseofulvin therapy,[10] this requires confirmation. The role of amorolfine as an adjuvant to oral therapy with an azole (e.g. itraconazole) or allylamine (e.g. terbinafine) antifungal has not been evaluated, and so cannot be recommended at present.

Another potential use for amorolfine in patients with onychomycosis is as an adjuvant following chemical or surgical nail avulsion. Once again, there is no evidence currently that amorolfine is effective in this situation.

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† Tioconazole nail paint is not available in Australia, Canada, Denmark, France or the US; bifonazole is not available in Australia or the US.

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Many avenues explored in search for herpes vaccines

Vaccine development may be the key to controlling herpes simplex virus (HSV), since attempts at eradicating the virus once infection is acquired have been universally unsuccessful. Advances in recombinant DNA technology have expanded the options available for vaccine development. Potential approaches include:

- live vaccines using either avirulent HSV strains, replication-incompetent viruses or avirulent carrier viruses expressing HSV glycoproteins
- killed HSV vaccines
- subunit vaccines
- genetic immunisation.[1]

In addition, vaccines are being evaluated both as primary protection against infection and as a means of reducing recurrent disease once infection has been acquired.

Vaccine development

Subunit vaccines

Subunit vaccines composed of HSV glycoproteins appear to have been most extensively evaluated to date, with some vaccines in phase III trials.

In preclinical trials, HSV-1 and HSV-2 glycoprotein vaccines have been shown to produce high antibody titres, prevent primary infection and protect against the establishment of latent infections in sensory ganglia.[2,3]

Administration of HSV-1 glycoprotein vaccines with immunostimulants such as interleukin-2 appears to enhance the protective efficacy of the vaccines.[4] This may be because these vaccines produce both humoral and cell-mediated immunity.[4]

Various other adjuvants have been evaluated, and shown to increase antibody titres and/or protection against infection.[5-7] These results have been confirmed in clinical trials. Among patients without evidence of infection with either HSV-1 or HSV-2, administration of a glycoprotein vaccine elicited both a positive antibody response and a strong cellular response.[8]

Antibody responses similar to those seen after natural infection were observed after 3 doses of vaccine in another trial. In addition, antibody responses were faster and cellular responses were longer-lasting when patients received the vaccine with an adjuvant (monophosphoryl lipid A).[8] Phase III studies of this vaccine are currently underway.[8]

However, despite promising immunological responses, studies using other HSV-2 glycoprotein vaccines have failed to prevent infection in patients at risk of acquiring genital HSV.[9,10]

Thus far, the only indication that subunit vaccines are of clinical benefit has come from a trial involving vaccination of patients with a history of recurrent genital herpes.[11] In these patients, 2 doses of vaccine reduced the median number of recurrent episodes from 6/year in placebo recipients to 4/year in vaccine recipients.[11] Means of enhancing the efficacy of this vaccine are being sought, since the prophylactic efficacy of vaccination in this trial was less than the protection offered by prophylactic aciclovir.[11]

Live vaccines

Live vaccines may include modified forms of HSV or use another virus expressing HSV glycoproteins as a vector. Vaccines using live vectors have not yet been evaluated in clinical trials.

Vaccines using vaccinia and adenovirus vectors have protected animals against primary infection.[1] In addition, intranasal administration of a recombinant adenovirus vector expressing glycoprotein B of HSV-1 has been shown to induce mucosal humoral and cell-mediated immunity in mice.[12] This may be important for protection against initial infection.[12]

Strains of HSV that do not cause disease have also been studied as potential vaccines, since prior infection with mutant viruses has been shown to protect animals against HSV infection.[1] However, the only avirulent virus vaccine evaluated in clinical trials to date appears to have poor immunogenicity.[1] Moreover, there is concern that mutant viral strains may revert to pathogenic strains.[1]

Another approach is to use HSV strains in which a gene essential for replication has been modified. These viruses are then incapable of replication, and cannot reactivate to produce infectious HSV even if latent infection becomes established.[1] In animal models of HSV-2, this type of vaccine provided 100% protection against primary disease when administered subcutaneously.[13] In addition, vaginal administration in animals with established HSV-2 infection reduced recurrence rates by 50%.[13]

Alternative approaches

Development of killed HSV vaccines has been relatively limited. Nonetheless, 2 killed HSV vaccines have been shown to be immunogenic in preliminary trials.[1]

A novel approach to conferring protection against infection is genetic immunisation. DNA or RNA encoding for a