Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Efinaconazole for Fungal Nail Infections: A Review of the Clinical Effectiveness, Cost-effectiveness, and Guidelines

DATE: 15 January 2016

CONTEXT AND POLICY ISSUES

Onychomycosis involves fungal infection of the nail bed, matrix or plate and represents about 50% of all nail disorders.[1] It occurs mostly in the toenails and less frequently in the fingernails, and can lead to deformity and destruction of the nail.[1] The main subtypes of onychomycosis include distal subungual onychomycosis, proximal subungual onychomycosis, and white superficial onychomycosis.[2] Onychomycosis is caused by dermatophyte fungi in about 90% of cases but can also be caused by yeast and molds.[3] Risk factors associated with onychomycosis include advanced age, tinea pedis, psoriasis, diabetes, immunodeficiency, and genetic predisposition.[2]

The prevalence estimates reported for onychomycosis are variable. One article[4] has mentioned that onychomycosis affects approximately 20% to 25% of world's population, though one has reported the prevalence estimate for onychomycosis to be in the range of 2% to 8% in westernized countries.[5] One article[6] reported a prevalence estimate for onychomycosis of 13.8% in the United States (US). A study conducted in Canada, with 15,000 patients visiting the offices of three dermatologists and one family physician, showed that 8% had onychomychosis.[2] These 8% onychomychosis patients were comprised of patients with toenail involvement (7.6%), patients with both fingernail and toenail involvement (0.27%) and patients with fingernail infection (0.15%).

Nail disorders due to onychomycosis are not always clinically distinguishable from nail disorders resulting from psoriasis, eczematous conditions, senile ischemia (onychogryphosis), trauma, lichen planus, iron deficiency, and other conditions. It is therefore useful to determine the presence of fungus before initiating antimycotic treatment.[2] Potassium hydroxide (KOH) examination of nail scrapings and fungal culture methods have been used to identify the fungus.[2]

Onychomycosis is sometimes perceived as a cosmetic problem and left untreated.[6] In addition, some may be unaware they have fungal infection and may not seek medical treatment.[7] If left

untreated, onychomycosis has the potential to result in additional morbidities such as wounds, cellulitis, secondary bacterial infection, pain, and difficulty with ambulation, especially for those with a compromised health condition.[7] Treatment of onychomycosis can be challenging for a number of reasons. Hyperkeratosis and/or the fungal mass may limit penetration of the drug to the infected area.[8] Prolonged treatment periods may be a deterrent to patient compliance.[8] Nail disorders due to onychomycosis are not always clinically distinguishable from nail disorders due to other reasons. Recurrence after treatment is not uncommon as residual hyphae or spores may have remained. Recurrence rates of onychomycosis are reported to be in the range of 10% to 53%.[7,8]

Treatment options for onychomycosis include oral agents (such as teribinafine, itraconazole, and fluconazole), topical agents (such as cicloprix, amorolfine, and efinaconazole), and laser therapy.[2] Efficacy data on laser therapy is limited and the optimal regimen to use is unclear. Oral agents have been found to be efficacious but are more likely to be associated with adverse effects and drug-drug interactions.[9] Topical agents have a low systemic absorption and so are less likely to be associated with adverse events but penetration through the nail plate can be an issue. New generation topical antifungals have been designed to have greater nail plate permeability. Efinaconazole is included in this group. On October 2013, Health Canada approved efinaconazole (10%) for the topical treatment of mild to moderate onychomycosis (tinea unguium) of toenails.[10] The US Federal Drug Administration (FDA) approved efinaconazole (10%) in 2014.[11]

Eficonazole is a triazole antifungal that inhibits fungal lanosterol 14α-demethylase involved in the ergosterol biosynthesis pathway. The accumulation of 14α-methyl sterols and subsequent loss of ergosterol in the fungal cell wall may be responsible for the antifungal activity of efinaconazole.[12]

The purpose of this report is to review the clinical efficacy and safety, and cost-effectiveness of efinaconazole for the treatment of fungal nail infections and to review the evidence-based guidelines regarding the treatment of fungal nail infections.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of efinaconazole for the treatment of fungal nail infections?

2. What is the cost-effectiveness of efinaconazole for the treatment of fungal nail infections?

3. What are the evidence-based guidelines regarding the treatment of fungal nail infections?

KEY FINDINGS

Compared to vehicle alone, efinaconazole resulted in greater complete cure or mycological cure rates in adults with mild to moderate onychomychosis. A network meta-analysis showed that for treatment of onychomychosis, oral antifungal agents ranked higher than topical antifungal agents with respect to mycological cure; and among the topical antifungal agents, efinaconazole ranked the highest. Safety issues were not investigated in the network meta-analysis.

No relevant economic studies of efinaconazole for the treatment of fungal nail infections were identified.

A Canadian guideline recommended an oral antifungal agent (teribinafine) for severe disease, oral teribinafine or topical antifungal agent (efinaconazole) for moderate disease and efinaconazole for mild disease. According to a guideline from the United Kingdom, teribinafine was recommended as first line therapy. This guideline mentioned that antifungals such as efinaconazole may be used, however the recommendation was mentioned to be of low strength.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, Medline, Embase, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. For research questions one and two no methodological filters were applied to limit the retrieval by study type. For research question three methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and December 7, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with fungal nail infection (Onychomycosis)
Intervention	Topical efinaconazole (e.g. Jublia)
Comparator	Other topical (e.g. ciclopirox) or oral (e.g. terbinafine, itraconazole, grisefulvin, fluconazole) treatment for fungal nail infections Placebo No treatment
Outcomes	Clinical effectiveness (e.g. improved fungal infection), safety and harms, cost-effectiveness, evidence-based guidelines
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), observational studies, economic studies and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2005. Studies investigating nail penetrance of efinaconazole without reporting on clinical outcomes were excluded. Studies investigating only pharmacokinetics were excluded. Articles on subgroup analyses of the included RCTs were excluded if the subgroups had not been determined a priori as patients in the subgroups can no longer be considered as randomly assigned which may impact comparability of the subgroups, the size of the subgroups may not be sufficient to detect a true difference, and unplanned subgroup analyses (those not determined a priori) are generally considered exploratory and could be a result of data dredging. Systematic reviews which included only studies that were already captured in an included systematic review were excluded. Systematic reviews that did not contain detailed information regarding trials were excluded. If information of the individual trials were available from trial reports, the trial reports were included instead. Guidelines on treatment of fungal nail infections that did not include efinaconazole or had unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR checklist;[13] the randomized controlled studies and observational studies were critically appraised using the Downs and Black checklist;[14] and guidelines were assessed with the AGREE II instrument.[15] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 136 citations were identified in the literature search. Following screening of titles and abstracts, 102 citations were excluded and 34 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 27 publications were excluded for various reasons, while seven publications[4,16-21] met the inclusion criteria and were included in this report. These comprised of one systematic review,[4] three RCTs,[16,20,21] one observational study,[19] and two evidence-based guidelines.[17,18] It should be noted that the main results of two RCTs were reported in a single publication[20] and additional details on these two RCTs were available in a second report.[16] Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that did not meet the selection criteria are provided in Appendix 7.

Summary of Study Characteristics

Characteristics of the included systematic review, RCTs and observational studies are summarized below and details are available in Appendix 2, Table A1 and A2.

Systematic Reviews

One relevant systematic review[4] was identified. It was published in 2015 from Canada. It compared therapies for onychomycosis, using a network meta-analysis with 19 parallel-group trials that were published between 1992 and 2013. These 19 trials included a total of 6,078 patients with onychomycosis of the toenails. The number of patients in the individual trials ranged between 31 and 1029. The extent of toenail involvement was not reported in nine trials and ranged between 37% and 65% in the remaining 10 trials. There were 15 placebo controlled trials (two trials with efinaconazole, two trials with fluconazole [150 to 450 mg, or 450 mg], two with ciclopirox, three trials with itraconazole [200mg], three trials with terbinafine [250 mg], and three trials with terbinafine nail solution [TNS]) and four active group trials (two trials for terbinafine [250 mg] versus itraconazole [200mg], one for itraconazole [200mg] versus itraconazole [400mg] and one for TNS versus amorolfine). In the trials, the outcome assessments were conducted at least 48 weeks after initiation of treatment. The outcome analyzed was mycologic cure rate. Mycologic cure rate was defined as negative potassium hydroxide test results and the absence of dermatophytes in culture.

Randomized Controlled Trials (RCTs)

Three relevant RCTs[20,21] were identified. Of these three RCTs, two were reported in a single report[20] with additional findings reported in a second report.[16] The RCTs were published in 2013 from U.S.A. All the RCTs were double-blinded, and conducted at multiple centers. One RCT[20] had centers in Canada, Japan and the USA., one RCT[20] had centers in Canada and the USA. and one RCT[21] had centers in Mexico. Of the three RCTs, two[20] were phase III studies and one[21] was a phase II study. The study duration was 52 weeks in two RCTs[20] and 40 weeks in one RCT.[21] The RCTs included patients with mild to moderate toenail onychomychosis. The number of included patients varied between 135 and 870, the mean age varied between 42.8 years and 52.3 years, and the proportion of females varied between 20% and 54%. The extent of toenail affected varied between 37% and 40%. The patient groups in each RCT were comparable with respect to age, gender and extent of toenail affected, as would be expected with randomization. Two RCTs[20] compared efinaconazole 10% with vehicle and one RCT compared two concentrations of efinaconazole (5% and 10%) with vehicle. All the RCTs reported on complete cure rates, mycologic cure rates, and adverse events. Quality of life (QoL) was reported for two of the RCTs in a separate report.[16] QoL was assessed using the OnyCOE-t questionnaire. It is a validated questionnaire specifically designed to measure patient reported outcomes associated with toenail onychomychosis. It should be noted that the two RCTs[20] on efinacinazole, which were included in the systematic review and network meta-analysis described above, are included in this section as well, as additional outcomes were reported in the RCT reports.[16,20]

Observational Study

One relevant observational study[19] was identified. It was published from U.S.A. in 2013. It was an open label, single-center, single-arm study investigating the pharmacokinetics and safety of efinaconazole. The study duration was 28 days. It included two groups of patients: healthy volunteers and patients with severe onychomychosis. Only information on the onychomycosis group, which is relevant for this report, is presented here. It included 20 patients with severe toenail onychomychosis. The age range of the patients was 21 years to 70 years. The proportion of male patients was 68.4%. Patients were treated with efinaconazole 10%. Adverse events were reported.

Guidelines

A description of the included guidelines is summarized below and details are available in Appendix 2, Table A3 and Appendix 3, Table A4.

Two relevant guidelines[17,18] for treatment of onychomycosis were identified. One guideline[17] was published from Canada in 2015 and one guideline[18] was published by the British Association of Dermatologists from the United Kingdom (U.K.) in 2014. Both guidelines were for management of onychomycosis. One guideline[17] was for assisting healthcare providers and patients to make informed decisions. One guideline[18] was for use in the clinic. One guideline[17] did not provide a grading system, while the other[18] provided a grading scheme for the level of evidence and the strength of recommendations. The level of evidence was graded from 1 to 4 with lower numbers indicating higher grade and the strength of recommendations was graded from A to D, with A indicating the greatest strength and then declining sequentially (Appendix 3, Table A4).

Summary of Critical Appraisal

Critical appraisal of the included systematic review, RCTs and observational studies is summarized below and details are available in Appendix 4, Tables A5 and A6.

Systematic Review

The included systematic review[4] was generally well conducted. The objective, and inclusion and exclusion criteria were stated. Multiple databases and trial registries were searched. It was unclear if article selection was done in duplicate. Data extraction was done by one reviewer and checked by a second reviewer. Descriptions of the individual studies were provided. Quality assessments of individual studies were conducted by two reviewers and were judged to be of good quality. It was not mentioned whether investigation of publication bias had been undertaken. However, as for each comparison there were few trials, exploration of publication bias may not have been feasible. Only one outcome (mycologic cure) was investigated; adverse events were not investigated.

Network meta-analysis was conducted. The network diagram was presented. The authors stated that the mean age of patients were similar across trials. It was unclear to what extent the studies included in analysis were comparable with respect to disease severity. The extent of toenail involvement ranged between 37% and 65% in 10 trials and was not reported for nine trials. In the network there was one closed loop and the node-splitting analysis showed there was consistency between indirect, direct, and overall comparison results. This closed loop however did not include efinaconazole. Also, there was not a common comparator for all the agents investigated. Convergence of the consistency model was reached after 20,000 tuning iterations and 50,000 simulation iterations, indicating that the model parameters and inputs were deemed appropriate for the purpose of this analysis.

Conflict of interest was declared. One author was an advisory board member, consultant, investigator and speaker for the manufacturer. The impact of this is however unclear.

RCTs

The three included RCTs[20,21] had clearly stated the objective, the inclusion criteria, and exclusion criteria and described the patient characteristics, interventions, and outcomes. In all three studies, randomization appeared to be appropriate; a computer generated schedule was used and allocation was concealed. The studies were double blinded. Discontinuation rates varied between 11% and 15% in the efinaconazole treated groups and between 18% and 21% for the vehicle treated groups. However, discontinuations for adverse events were less than 5%. Reasons for discontinuation were mainly adverse events, patient request, protocol violation, or lost to follow up. Generalizability of the findings is limited. The studies were conducted under controlled conditions and in adults with mild to moderate onychomychosis. It is possible that patients who agreed to participate in the trials were more likely to be compliant than patients generally seen in real world practice. It is unclear to what extent the findings would be applicable to patients with severe onychomycosis. All three RCTs were sponsored by the manufacturer and most of the investigators were associated with the manufacturer, hence the potential for bias cannot be ruled out.

Observational Study

The included observational study[19] had clearly stated the objective, the inclusion criteria and exclusion criteria and described the patient characteristics, interventions and outcomes. It was a single center, non-randomized study with a single treatment group and no comparator group. One patient discontinued prior to administration of treatment. Generalizability of the findings is limited. The study was on patients with severe onychomycosis so it is unclear how patients with less severe disease would respond. With no comparator group it is unclear to what extent the response can be attributed to the drug itself. The study was sponsored by the manufacturer and most of the investigators were associated with the manufacturer, hence the potential for bias cannot be ruled out.

Guidelines

Critical appraisal of the included evidence-based guidelines is summarized below and details are available in Appendix 4, Table A7.

The included guidelines[17,18] clearly stated the scope and purpose. For both guidelines, the guideline development group was composed of individuals from relevant areas such as dermatology and the methodology used for guideline development appeared to be rigorous; a systematic review of the literature was undertaken. For both guidelines it was unclear if patient input had been sought. One guideline[17] mentioned cost implications and one guideline[18] did not. One guideline[18] graded the recommendations and one guideline[17] did not. Both guidelines were internally and externally reviewed. Conflict of interest was disclosed and for one guideline,[18] two of the five authors were associated with industry and for one guideline,[17] all 10 authors were associated with industry.

Summary of Findings

What is the clinical effectiveness and safety of efinaconazole for the treatment of fungal nail infections?

Findings are summarized below and details are provided in Appendix 5, Tables A8 and A9.

Systematic Review

The included systematic review and network meta-analysis showed that the oral agents were better than the topical agents with respect to mycological cure. According to the network meta-analysis, the individual agents were ranked in the following order with Rank 1 indicating best in the group: terbinafine, 250 mg (Rank 1); itraconazole, 400 mg, pulse (Rank 2); itraconazole, 200 mg (Rank 3); fluconazolr (Rank 4); efinaconazole (Rank 5); cicloprix (Rank 6); terafinabine nail solution (Rank 7); amorolfine (Rank 8); and placebo (Rank 9). However, adverse effects of these agents had not been examined.

Randomized controlled trial

The three included RCTs[20,21] showed that complete cure was greater with efinaconazole than vehicle (Table 2). In two RCTs[20] the differences were reported to be statistically significant ($P < 0.001$) and in one RCT[21] statistical significance was not reported. Complete cure was defined as zero percent clinical involvement of the target toenail in addition to mycologic cure. Mycologic cure was defined as a negative potassium hydroxide test as well as a negative fungal culture of the toenail. Two RCTs[20] showed statistically significantly higher mycologic cure with efinaconazole compared with vehicle. The complete cure rate and the mycologic cure rate with efinaconazole were both higher in one RCT[21] compared to that in the other two RCTs[20] (Table 2). This difference in cure rates may be due to the differences in the patient composition. The mean age of patients in the efinaconazole group was 43 years in one RCT,[21] and 52 years (Study 1) and 51 years (Study 2) in the other two RCTs.[20] The proportion of females in the efinaconazole group was 54% in one RCT,[21] and 26% (Study 1) and 20% (Study 2) in the other two RCTs.[20] Quality of life (QoL) data for the two RCTs (Study 1 and Study 2) were reported in a separate publication[16] and were shown to be statistically significantly (P in the range 0.002 to < 0.001) better with efinaconazole compared with vehicle, with respect to various items such as symptom frequency, symptom bothersomeness, and problems with physical activity as measured using the OnyCOE-t questionnaire. Details are available in Appendix 5, Table A9. Adverse events were similar in the efinaconazole and vehicle treatment arms and were generally of mild or moderate severity. The rates of discontinuation due adverse events were low (3.2% versus 0.5%, 1.9% versus 0% and 2.6% versus 4.5% for efinaconazole versus vehicle).

Table 2: Efficacy data

Outcome	Intervention	Percentage of patients with the outcome		
		Elewski et al.[20]		Tschen et al.[21]
		Study 1 (N = 656 for E, N = 214 for V)	Study 2, (N = 583 for E, N = 202 for V)	(N = 39 for E, N = 22 for V)
Complete cure	Efinaconazole 10%	17.8	15.2	25.6
	Vehicle	3.3	5.5	9.1
Mycologic cure	Efinaconazole 10%	55.2	53.4	87.2
	Vehicle	16.8	16.9	NR

N = total number of patients treated in the efinaconazole (E) arm or vehicle (V) arm

Observational study

One included observational study[19] investigated safety in 20 patients with severe onychomycosis and reported that none of the adverse events encountered were serious or

related to the efinaconazole. Four patients experienced adverse events such as upper respiratory tract infection, skin laceration, arthralgia, and back pain during the study. Some patient (10%) reported burning and/or itching but these were not considered adverse events.

What is the cost-effectiveness of efinaconazole for the treatment of fungal nail infections?

No economic evaluations of efinaconazole for the treatment of fungal nail infections were identified.

What are the evidence-based guidelines regarding the treatment of fungal nail infections?

Recommendations from included evidence-based guideline recommendations are summarized below and details are available in Appendix 6, Table A10

According to one guideline[17] from Canada, treatment for onychomycosis is based on the extent of nail plate involvement. For > 60% involvement (i.e. severe condition) terbinafine was recommended, for 20% to 60% involvement efinaconazole or terbinafine may be used, and for < 20% involvement efinaconazole may be used. Alternative oral or topical antifungal agents may be needed depending on comorbidities, nail thickness, patient adherence and patient preference.

One guideline[18] from U.K., recommended terbinafine or itraconazole as first line treatment for adults with fungal nail infection, with terbinafine being preferred over itrconazole (strength of recommendation: A). Fluconazole was recommended as an alternative if patients were intolerant to terbinafine or itraconazole (strength of recommendation: B). Hepatic monitoring was recommended with these treatment modalities. It was suggested that griseoflavin may also be used for treatment of fungal nail infection (strength of recommendation: C). Topical antifungal agents (amorolfine, ciclopirox, ticonazole or efinaconazole) may also be used (strength of recommendation: D).

Limitations

In the included RCTs, efinaconazole was compared with vehicle (no active agent). No studies on the direct comparison of efinaconazole with other active agents for treating fungal infection of the nail were identified. However, several antifungal agents including efinaconazole, were indirectly compared using a network meta-analysis. This analysis examined only one outcome (mycological cure) and did not examine any safety issues. Hence the balance between benefit and harm could not be determined.

It should be noted that in the included systematic review with the network meta-analysis, the two efinaconazole RCTs used are two of the RCTs also included in this report.

Generalizability of the findings is limited. Most of the RCTs were on adults with mild to moderate disease. RCTs entail controlled conditions, hence it is unclear to what extent the results from the RCTs can be extrapolated to the real world situation of general practice. All the included studies were on treatment of toenails with efinaconazole, hence it is unclear to what extent the findings would be applicable for finger nails.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Seven relevant publications were identified. These were comprised of one systematic review with network meta-analysis, three RCTs, one observational study and two guidelines.

Compared to vehicle, efinaconazole resulted in greater complete cure or mycological cure in adults with mild to moderate onychomychosis. Discontinuations due to adverse events were few. A network meta-analysis showed that for treatment of onychomychosis, oral antifungal agents ranked higher than topical antifungal agents with respect to mycological cure; and among the topical antifungal agents, efinaconazole ranked the highest. Safety issues were not investigated by network meta-analysis.

No relevant economic studies of efinaconazole for the treatment of fungal nail infections were identified.

A Canadian guideline recommended an oral antifungal agent (teribinafine) for severe disease, oral teribinafine or topical antifungal agent (efinaconazole) for moderate disease and efinaconazole for mild disease. According to a guideline from the United Kingdom, teribinafine was recommended as first line therapy. This guideline mentioned that antifungals such as efinaconazole may be used, however the recommendation was mentioned to be of strength D (low).

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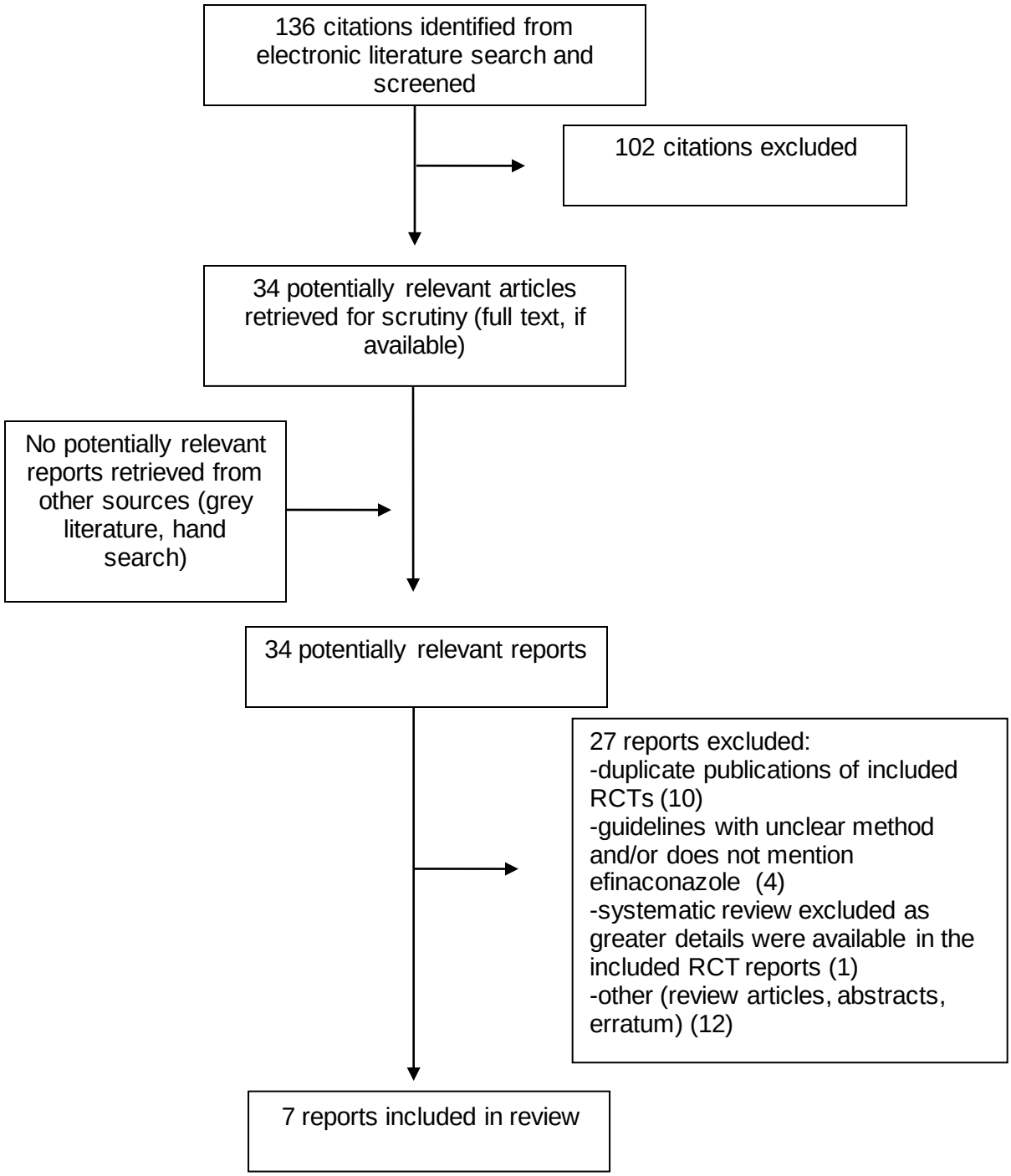
ABBREVIATIONS

AE	Adverse event
DB	double blind
DLSO	distal lateral subungual onychomychosis
E	efinaconazole
N	total number of patients
NA	not applicable
NR	not reported
QoL	quality of life
RCT	randomized controlled trial
TEAE	treatment emergent adverse event
U.K.	United Kingdom
U.S.A.	United States of America
V	vehicle

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics[a]	Comparisons[a]	Clinical Outcomes, Length of Follow-Up
Gupta,[4] 2015, Canada	Systematic review with NMA. 19 RCTs were included	Adults with onychomychosis of toenails Number of patients in individual RCTs ranged between 31 and 1029 Age (years): Mean age varied between 41 and 44 (14), Age range of 42 to 47 (1), Age range of 18 to 70 (1), Age ≥18 (2), Age not reported (1)	Efinaconazole vs plb (2) Flucanozole vs plb (2) Terifinabine nail solution vs plb (3) Ciclopirox vs plb (2) Terifinabine vs plb (3) Itracohnazole, 200 mg vs plb (3) Itraconazole, 200 mg vs Itraconazole, 400 mg (1) Itraconazole, 200 mg vs Terafinabine (2) Terifinabine nail solution vs Amorolfine (1)	Mycological cure[b] Outcome assessment at least up to 48 weeks from initiation of treatment

plb = placebo, RCT = randomized controlled trial, vs = versus
[a]The number in parenthesis indicates the number of studies for that particular comparison
[b]Mychological cure w as defined as negative potassium hydroxide test results, and the absence of dermatophytes in culture

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Randomized controlled trials					
Elewski,[20] 2013, U.S.A	Phase III, DB, RCTs (Study 1 and Study 2), multi-center (118 centres). Study 1 (at (Canada, Japan and U.S.A.), Study 2 (at Canada and	Patients with mild to moderate toenail DLSO[a] N = 1,655 (Study 1: 870, Study 2: 785) Age (year) (mean [range]): Study 1: 52.3	Efinaconazole 10%	Vehicle	Complete cure, mycologic cure, adverse events. QoL[b]

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
	U.S.A) Duration: 52 weeks (treatment was for 48 weeks with 4-week post-treatment follow up)	[18.0 to 71.0], Study 2: 50.6 (18.0 to 71.0] % Female: Study 1: 25.6% Study 2: 19.6%			
Tschen,[21] 2013, U.S.A	Phase II DB RCT, multicenter (at Mexico) Duration: 40 weeks (treatment was for 36 weeks with 4-week post-treatment follow up)	Patients with mild to moderate toenail DLSO N = 135 Age (year) (mean [range]): 42.8 [19 to 64] % Female: 54.1%	3 groups: Efinaconazole 10% (with semiocclusion), Efinaconazole 10%, Efinaconazole 5%	Vehicle	Complete cure, mycologic cure, adverse events.
Observational study					
Jarratt,[19] 2013, U.S.A	Open label single center, single arm study. Duration 28 days	Patients with severe toenail onychomycosis.[c] N = 20 Age (year) (range): 21 to 70 % Mate: 68.4%	Efinaconazole 10%	NA	Adverse events

DB = double blind, DLSO = distal lateral sunungual onychomychosis, N = number of patients, NA = not applicable, RCT = randomized controlled trial, U.S.A. = United States of America

[a]Mild to moderate DLSO defined as 20% to 50% clinical involvement of the target toenail, without dermatophytomas or matrix (lunula) involvement

[b]Data from report by Tosti and Elewski[16]

[c]This study examined two groups: healthy volunteers and patients with onychomychosis. Only information on the onychomychosis patients which is the patient group relevant for this report, are included here

Table A3: Characteristics of Included Guidelines	
Objectives	**Methodology**
Gupta,[17] 2015, Canada	
Development of a clinical pathway for toenail onychomycosis – a Canadian approach	Guidelines were developed by an expert panel using a modified Delphi process. Multiple databases were searched from January 2000 to November 2013. Only English language articles were included. A systematic review of the literature was conducted. Based on the results a survey was designed to determine consensus regarding the treatment pathway. Recommendations were not graded. Guidelines were reviewed by the panel members and also externally reviewed during journal publication. Future proposal for updating the guideline was not mentioned.
British Association of Dermatologists; Ameen,[18] 2014, U.K.	
Recommendations for use in clinic for management of patients with onychomycosis	Guidelines were developed using the BAD's methodology [22] and with reference to the AGREE II tool. Multiple databases were searched from January 2002 to February 2014. Reference lists of relevant articles were searched. Only English language articles were included. It was mentioned that a detailed appraisal of the relevant literature was conducted. Recommendations were graded. Guidelines were reviewed internally and externally. Update of guideline proposed for 2019 and if necessary interim changes will be updated on the BAD website.

BAD = British Association of Dermatologists, U.K. = United Kingdom

APPENDIX 3: Grading of Recommendations and Levels of Evidence

Table A4: Grading of Recommendations and Levels of Evidence

Guideline Society and/or Author, Year, Country, Topic	Recommendation grade and Level of Evidence
British Association of Dermatologists; Ameen,[18] 2014, U.K. Guidelines for the management of onychomycosis	**Recommendation Strength:** "A At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal B A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+ C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++ D Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus D (GPP) A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group" Page 958 **Levels of Evidence:** "1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias 2++ High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Table A4: Grading of Recommendations and Levels of Evidence	
Guideline Society and/or Author, Year, Country, Topic	**Recommendation grade and Level of Evidence**
	2- Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal 3 Nonanalytical studies (for example case reports, case series) 4 Expert opinion, formal consensus" Page 958

NICE = National Institute for Health and Care Excellence, RCT = randomized controlled trial

APPENDIX 4: Critical Appraisal of Included Publications

Table A5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR checklist[13]

Strengths	Limitations
Gupta,[4] 2015, Canada	
• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases were searched, search time frame was before March, 2013. Clinical trial registries were searched. • Study selection was described and a flow chart was presented • List of included studies was provided • Data extraction was performed by one reviewer and checked by a second reviewer • Methodological quality of the included trials were assessed by two reviewers An onychomycosis study quality assessment tool developed by the authors were used.[23] All the included studies were judged to be of good quality (each study had a score of 11 or more on a scale of zero to 20) • Network meta-analysis was conducted and appeared to be appropriate. The network diagram was presented. In the network there was one closed loop and the node-splitting analysis showed there was consistency between indirect, direct and overall comparison results. Convergence of the consistency model was reached after 20,000 tuning iterations and 50,000 simulation iterations. • Conflict of interest was declared. One author was an advisory board member, consultant, investigator and speaker for the manufacturer	• List of excluded studies was not provided • Unclear if article selection was done in duplicate • There was no mention of exploration of publication bias

Table A6: Strengths and Limitations of Randomized Controlled Trials and Observational Studies using Downs and Black Checklist[14] [i]

Strengths	Limitations
Randomized controlled trials (RCTs)	
Elewski,[20] 2013, U.S.A	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described • Double blind, randomized study (Computer generated randomization schedule; schedule not accessible till the both the database was locked and the study unblinded) • Number discontinued were reported and reasons for discontinuation were reported • *P*-values were provided • Conflicts of interest were declared. Majority of the authors had associations with the manufacturer	• Sample size calculation was not provided • Number of patients discontinuing varied between 12% and 20%. In Study 1, the number of patients discontinued was similar in both arms (12.3% and 12.6%) but in Study 2 more discontinued in the vehicle arm (21%) compared to the efinaconazole arm (15%).Impact of this is unclear. • The study was supported by the manufacturer • Generalizability limited to the study population
Tschen,[21] 2013, U.S.A	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described • Double blind, randomized study (Computer generated randomization schedule; schedule not accessible till the database was locked and the study unblinded) • Number discontinued were reported and reasons for discontinuation were reported • *P*-values were provided for outcomes but not for adverse event. • Conflicts of interest were declared. Majority of the authors had associations with the manufacturer	• Sample size calculation was not provided • Number of patients discontinuing varied between 11% and 15% for the efinaconazole treated groups and 18% for the vehicle treated group. • The study was supported by the manufacturer • Generalizability limited to the study population
Observational study	
Jarratt,[19] 2013, U.S.A	
• Objectives were clearly stated. • Inclusion criteria were stated • Patient characteristics, intervention and outcomes were described • Number discontinued was reported and reason for discontinuation was reported. One patient discontinued prior to first application • Conflicts of interest were declared. Majority of the authors had associations with the manufacturer	• Exclusion criteria were not explicitly stated. • Non-randomized study; open label, single center, single arm (no comparator) • *P* values for adverse events were not provided • The study was supported by the manufacturer • Generalizability limited to the study population

Table A7: Strengths and Limitations of Guidelines using AGREE II[15]

Strengths	Limitations
Gupta,[17] 2015, Canada	
• The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas (such as dermatologists, general practitioners, podiatrists, and chiropodists). • The methods used for the development of the guidelines appear to be rigorous (multiple database searched, systematic review conducted). The expert panel used a modified Delphi process for the developing the clinical care pathway. • Internal (panel members) and external (journal publication) reviews of the guidelines were conducted. • Cost implications, and healthcare system and societal perspectives were considered. • Conflicts of interest of guideline development group members were stated. All authors were associated with industry	• Unclear if patient input was sought. • Recommendations were not graded.
British Association of Dermatologists; Ameen,[18] 2014, U.K.	
• The scope and purpose were clearly stated. • The guideline development group comprised of individuals from relevant areas (consultant dermatologists and a consultant mycologist). • The guidelines were developed using the BAD's methodology[22] and with reference to the AGREE II tool. • Internal and external reviews of the guidelines were conducted. • Recommendations were graded. • Conflicts of interest of guideline development group members were stated. Two of the authors were associated with industry.	• Cost implications or organizational barriers were not discussed. • Unclear if patient input was sought.

APPENDIX 5: Main Study Findings and Author's Conclusions

Table A8: Summary of Findings of the Systematic Review

Main Study Findings and Author's Conclusions

Gupta,[4] 2015, Canada

Main Findings:

Odds Ratio (OR) for Mycological Cure with Efinaconazole versus Other Onychomychosis Treatments

Treatment	Type	OR (95% CrI) for Efinaconazole, 10% versus other treatments
Teribinafine, 250 mg	Oral	0.13 (0.06 to 0.28)
Itraconazole, 400 mg, Pulse	Oral	0.33 (0.10 to 1.22)
Itraconazole, 200 mg	Oral	0.37 (0.16 to 0.79)
Fluconazole, 150–450 mg	Oral	0.65 (0.31 to 1.41)
Ciclopirox 8%	Topical	1.41 (0.65 to 2.99)
Terbinafine nail solution	Topical	1.44 (0.71 to 2.85)
Amorolfine 5%	Topical	1.48 (0.59 to 3.60)
Placebo	Oral or topical	5.90 (3.83 to 9.23)
CrI = credible interval, OR = odds ratio		

Ranking of Treatments Based on the Probability of Mycological Cure

Treatment	Rank of treatment	Probability of achieving the rank for mycological cure with the treatment	Range of probabilities of achieving the rank for mycological cure for the remaining treatments
Teribinafine, 250 mg	1	0.96	0.00 to 0.03
Itraconazole, 400 mg, Pulse	2	0.55	0.00 to 0.35
Itraconazole, 200 mg	3	0.59	0.00 to 0.26
Fluconazole, 150–450 mg	4	0.67	0.00 to 0.11
Efinaconazole	5	0.61	0.00 to 0.12
Ciclopirox 8%	6	0.34	0.00 to 0.26
Terbinafine nail solution	7	0.43	0.00 to 0.30
Amorolfine 5%	8	0.37	0.00 to 0.34
Placebo	9	1.00	0.00

Authors' Conclusions:

"Terbinafine, 250 mg, therapy was significantly superior to all treatments except itraconazole, 400 mg, pulse therapy; …… and fluconazole, efinaconazole, ciclopirox, terbinafine nail solution, and amorolfine treatments were significantly superior to only placebo. ……. These results reflect findings from the literature and treatment efficacy observed in clinical practice." Page 357

Table A9: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Randomized controlled trials

Elewski,[20] 2013, U.S.A

Main Findings:

Efficacy of efinaconazole (E) versus vehicle (V) for treatment of onychomycosis

Outcome at 52 week	Proportion of patients with the outcome (%)				*P* value for E versus V for both studies
	Study 1		Study 2		
	E N = 656	V N = 214	E N = 583	V N = 202	
Complete cure (primary outcome)	17.8	3.3	15.2	5.5	< 0.001
Mycologic cure	55.2	16.8	53.4	16.9	< 0.001
Complete or almost complete cure	26.4	7.0	23.4	7.5	< 0.001
Treatment success (<10% clinical involvement)	35.7	11.7	31.0	11.9	< 0.001
Treatment success (≤10% affected toe nail area)	45	17	40	15	NR
Treatment success (≤ 5% affected toe nail area)	35	11	29	11	NR
Treatment success (0% affected toe nail area)	21	6	18	7	NR

E = efinaconazole, N = number of patients, NR = not reported, V = vehicle

Treatment-emergent adverse events (TEAE) with efinaconazole (E) versus vehicle (V) for treatment of onychomycosis (safety population)

Adverse events	Proportion of patients with adverse events (%)			
	Study 1		Study 2	
	E N = 653	V N = 213	E N = 574	V N = 200
≥ 1 TEAE	660.0	61.0	64.5	58.5
Individual TEAEs reported by ≥ 2% of patients in at least one study				
Application site dermatitis	3.5	0.0	NR	NR
Application site vesicles	2.0	0.0	1.2	0.0
Arthralgia	2.0	3.3	3.1	1.0
Back pain	2.5	2.8	3.3	3.5
Increased blood creatinine phosphokinase	NR	NR	1.9	2.5
Bronchitis	1.2	1.9	2.4	1.5
Contact dermatitis	2.9	1.9	1.4	1.0
Eczema	3.4	3.3	NR	NR
Folliculitis	0.8	2.3	NR	NR
Headache	2.3	2.3	4.4	3.5
Hypertension	2.6	4.7	1.9	2.5
Influenza	2.5	3.8	1.7	0.5
Ingrowing nail	2.6	0.5	1.9	1.0
Nasopharyngitis	11.9	11.7	11.0	7.5
Procedural pain	1.5	3.3	1.0	0.0
Sinusitis	4.6	1.9	3.0	2.5
Tinea pedis	1.1	2.8	0.7	3.0
Upper respiratory tract infection	5.8	6.1	6.1	5.5
Urinary tract infection	1.8	3.8	2.1	1.0

E = efinaconazole, N = number of patients, NR = not reported, V = vehicle

Table A9: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Reason for discontinuation	Number (%) of patients with discontinuing			
	Study 1		Study 2	
	E N = 656	V N = 214	E N = 583	V N = 202
Adverse event	21 (3.2)	1 (0.5)	11 (1.9)	0
Patient request	31 (4.7)	12 (5.6)	36 (6.2)	19 (9.4)
Protocol violation	20 (3.0)	1 (0.5)	3 (0.5)	3 (1.5)
Lost to follow up	-	11 (5.1)	29 (5.0)	18 (8.9)
Other	9 (1.4)	2 (0.9)	5 (0.9)	2 (1.0)

E = efinaconazole, N = number of patients, V = vehicle

Authors' Conclusions:

"Once daily topical efinaconazole appears to be a viable alternative to oral treatment options for onychomychosis." Page 600

QoL data for theses 2 RCTs were reported in a separate article by Tosti and Elewski[16] and are presented below

Main Findings:

Treatment with efinaconazole 10% compared with vehicle: QoL evaluation using OnyCOE-t questionnaire

Item	Mean change in domain score from baseline to week 52 (standard deviation)		Difference in change score between E and V groups	*P* value
	E N = 1,236	V N = 415		
Symptom frequency	26.5 (24.0)	16.2 (25.6)	10.4	< 0.001
Symptom bothersomeness	17.8 (23.2)	10.9 (25.3)	6.9	< 0.001
Physical activities problems	17.5 (27.4)	11.5 (25.9)	6.0	0.002
Appearance problems	22.6 (24.9)	14.9 (25.2)	7.7	< 0.001
Overall problem	28.0 (33.5)	17.1 (33.1)	10.9	< 0.001
Stigma	9.2 (21.6)	4.3 (19.4)	4.9	0.002

E = efinaconazole, V = vehicle

QoI of patients treated with efinaconazole 10%, according to extent of clinical improvement

Item	Mean change in domain score from baseline to week 52 (standard deviation)		Difference in change score between the two groups
	Clinically improved (i.e. ≤ 10% nail involvement) N = 527	Clinically not improved N = 709	
Symptom frequency	32.2 (22.5)	22.1 (24.2)	10.1
Symptom bothersomeness	22.1 (23.4)	14.9 (22.7)	7.2
Physical activities problems	21.2 (28.0)	14.6 (26.6)	6.6
Appearance problems	26.8 (25.0)	19.3 (24.4)	7.5
Overall problem	33.7 (35.0)	23.5 (31.7)	10.2
Stigma	9.3 (23.4)	9.1 (20.1)	0.2

Table A9: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Note:
The OnyCOE-t questionnaire comprised 33 items, grouped into multi- or single-item scales. All items in the OnyCOE-t questionnaire were transformed to a 0 to 100 scale and higher scores indicated better functioning.

Authors' Conclusions:
"Once-daily efinaconazole topical solution, 10%, provided statistically greater improvement in all aspects of quality of life compared to vehicle. Improvement was most marked in those patients considered clinically improved and correlated with a change in percent affected nail." Page 25

Tschen,[21] 2013, U.S.A

Main Findings

Efficacy of various concentrations of efinaconazole (E) versus vehicle (V) for treatment of onychomycosis (treatment duration: 36 months)

Outcome at follow up (40 week)	Proportion of patients with the outcome (%)			
	E (10% with semiocclusion) N = 36	E (10% without semiocclusion) N = 39	E (5% N = 38	V N = 22
Complete cure	22.2	25.6	15.8	9.1
Mycologic cure	83.3	87.2	86.8	NR
Mycologic cure and either an affected target toenail area of 0% or >3 mm proximal nail growth from baseline in the unaffected target toenail	61 (P = 0.0041)[a]	64 (P = 0.0030)[a]	55 (P = 0.0158)[a]	23
< 20% of the affected target toenail	67 (P = 0.0088)[a]	69 (P = 0.0064)[a]	NR	32

E = efinaconazole, N = number of patients, NR = not reported, V = vehicle
[a]P value of active agent versus vehicle

Adverse events with various concentrations of efinaconazole (E) versus vehicle (V) for treatment of onychomycosis

Variable	E (10% with semiocclusion) N = 36	E (10% without semiocclusion) N = 39	E (5% N = 38	V N = 22
Patients with TEAE, n (%)	25 (69.4)	30 (76.9)	25 (65.8)	14 (63.6)
Discontinued study medication due to TEAE, n (%)	0	1 (2.6)	1 (2.6)	1 (4.5)
Adverse events, n	85	74	72	40
Serious TEAE (not all related), n (%)	4 (4.7)	1 (1.4)	2 (2.8)	0
TEAE related to study drug, n (%)	0	1 (1.4) (in growing toe nail)	3 (4.2) (blister-1, contact dermatitis -1, erythema-1)	0

E = efinaconazole, n = number of events or number of patients with event, N = number of patients, TEAE = treatment emergent adverse event, V = vehicle

Table A9: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Discontinuation of treatment with efinaconazole (E) or vehicle (V)

Reason for discontinuation	Number of patients discontinuing			
	E (10% with semiocclusion) N = 36	E (10%) N = 39	E (5%) N = 38	V N = 22
Adverse event	-	1	1	1
Patient request	-	2	-	1
Protocol violation	-	1	1	-
Lost to follow up	4	1	2	1
Other	-	1	-	1

E = efinaconazole, N = number of patients, V = vehicle

Authors' Conclusions

"This study provided evidence that once daily efinaconazole 10% solution (with or without semiocclusion) applied topically for 36 weeks was more effective than vehicle in treating DLSO and was well tolerated. Based on these results, efinacinazole 10% solution was chosen for the phase 3 development program." Page 186

(DLSO = distal lateral subungual onychomychosis)

Observational study

Jarratt,[19] 2013, U.S.A

Main Findings

Four patients with onychomycosis experienced at least one adverse event which included upper respiratory tract infection, skin laceration, arthralgia, and back pain. However they were not considered to be serious or related to the study drug. One patient reported mild redness on applying efinaconazole on day 7. Burning and/or itching were experienced by 10% of patients; these were however not considered by the investigators as adverse events. All adverse events were resolved with or without the use of concomitant therapy.

Authors' Conclusions

"Efinaconazole 10% solution was well tolerated when topically applied to toenails of healthy volunteers and onychomychosis patients." Page 1014 -1015.

APPENDIX 6: Guidelines and Recommendations

Table A10: Summary of Guidelines and Recommendations

Gupta,[17] 2015, Canada

A Canadian treatment pathway for toenail onychomycosis

Treatment for toenail onychomycosis is based on the percentage of nail involvement.
For > 60% involvement (severe condition) oral terbinafine is recommended.
For 20% to 60% involvement topical efinaconazol ± terbinafine is recommended.
For < 20% involvement topical efinaconazol is recommended. This may be combined with selective debridement or with oral terbinafine.
Treatment with alternative oral or topical antifungal agents may be needed depending on comorbidities, nail thickness, patient preference or patient adherence.

British Association of Dermatologist; Ameen, 2014,[18] U.K.

Guidelines and Recommendations for the Management of Onychmycosis in Adults

Recommendation Strength	Treatment	Dosage and monitoring	Contraindications and cautions
A	Itraconazole (systemic therapy) as first line treatment	"200 mg per day for 12 weeks continuously, or alternatively as 'pulse therapy' at a dose of 400 mg per day for 1 week per month. Two pulses are recommended for fingernails and three pulses for toenails. It is optimally absorbed with food and an acidic pH. Monitoring hepatic function tests is recommended in patients with preexisting deranged results, in those receiving continuous therapy for more than a month, and with concomitant use of hepatotoxic drugs." Page 951	Heart failure, hepatotoxicity
A	Terbinafine (systemic therapy) as first line treatment and generally preferred over itraconazole	"250 mg per day for 6 weeks in fingernail and 12–16 weeks in toenail infection Baseline liver function tests and a complete full blood count are recommended in adult patients with a history of hepatotoxicity or haematological abnormalities" Page 951	Hepatic impairment, renal impairment
B	Fluconazole (systemic therapy) as an alternative for patients unable to tolerate terbinafine or itraconazole	"150–450 mg per week for 3 months in fingernail infections and for at least 6 months in toenail infections Perform baseline liver function tests and full blood count. Monitor liver function tests in high-dose or prolonged therapy and in those at risk because of concomitant hepatotoxic drug use" Page 951	Hepatic impairment, renal impairment
C	Griseofulvin (systemic therapy; compared to	"500–1000 mg per day given for 6–9 months in fingernail infection and 12–18 months in toenail infection. It should be	Liver impairment

Table A10: Summary of Guidelines and Recommendations

	itraconazole or terbinafine it has lower efficacy and higher relapse rates)	taken with fatty food to increase absorption" Page 951	
D	Combination treatment in case response to topical monotherapy is likely to be poor	NR	NR
D	Amorlofine (topical) useful for superficial and distal onychomycosis	"5% lacquer applied once or twice a week for 6–12 months" Page 951	NR
D	Ciclopirox (topical) useful for superficial and distal onychomycosis and for those with contraindication to systemic therapy	"8% lacquer applied once daily for up to 48 weeks" Page 951	NR
D	Tioconazole useful for superficial and distal onychomycosis	"28% solution applied twice daily for 6–12 months" Page 951	NR
D	Efinaconazole	10% solution, once daily	NR

APPENDIX 7: Additional References of Potential Interest

Systematic review mentioning RCTs that are included in the current report:
(Note: RCT reports included more relevant details and were therefore included instead of the systematic review)

Gupta AK, Daigle D, Foley KA. Topical therapy for toenail onychomycosis: an evidence-based review. Am J Clin Dermatol. 2014 Dec;15(6):489-502.

Pooled results of two RCTs included in the current report:

Joseph WS, Vlahovic TC, Pillai R, Olin JT. Efinaconazole 10% solution in the treatment of onychomycosis of the toenails. J Am Podiatr Med Assoc. 2014 Sep;104(5):479-85.

Subgroup analyses of included RCTs not defined a priori:

Bhatia N. Managing assessments and expectations: patient responses following therapy with efinaconazole topical solution, 10%. J Drugs Dermatol. 2015 Jul;14(7):694-8.

Gupta AK, Elewski BE, Sugarman JL, Ieda C, Kawabata H, Kang R, et al. The efficacy and safety of efinaconazole 10% solution for treatment of mild to moderate onychomycosis: a pooled analysis of two phase 3 randomized trials. J Drugs Dermatol. 2014 Jul;13(7):815-20.

Jellinek NJ, Korotzer A. Prognostic factors for complete cure following treatment of mild and moderate toenail onychomycosis with efinaconazole topical solution 10. J Drugs Dermatol. 2015 Aug;14(8):871-5.

Markinson B, Caldwell B. Efinaconazole topical solution, 10% efficacy in patients with onychomycosis and coexisting tinea pedis. J Am Podiatr Med Assoc. 2015 Sep;105(5):407-11.

Rich P. Efinaconazole topical solution, 10%: the benefits of treating onychomycosis early. J Drugs Dermatol. 2015 Jan;14(1):58-62.

Rodriguez DA. Efinaconazole topical solution, 10%, for the treatment of mild and moderate toenail onychomycosis. J Clin Aesthet Dermatol [Internet]. 2015 Jun [cited 2015 Dec 15];8(6):24-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4479366

Rosen T. Evaluation of gender as a clinically relevant outcome variable in the treatment of onychomycosis with efinaconazole topical solution 10. Cutis. 2015 Sep;96(3):197-201.

Vlahovic TC, Joseph WS. Efinaconazole topical, 10% for the treatment of toenail onychomycosis in patients with diabetes. J Drugs Dermatol. 2014 Oct;13(10):1186-90.

Guideline with no methodology details:

Gupta AK, Paquet M. Management of onychomycosis in Canada in 2014. J Cutan Med Surg. 2015 May;19(3):260-73.