International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

# Assessment of the Effectiveness of Combination of Systemic and Topical Antifungals against Monotherapy with Either One in Onychomycosis

Hephzeeba Joyce[*1], Anjitha.S.Kumar[2], Prasobh.G.R[3]
[1,2] *Pharm D students, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala, India.*
[3] *Principal, Head of department of pharmacy practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala, India.*

Date of Submission: 10-08-2021 Date of Acceptance: 29-08-2021

**ABSTRACT**
Onychomycosis (Tineaunguium) is the common disorder which affects the nail unit, caused by the fungus. Now a days most common disease is diabetes mellitus, one of the basic risk factor for onychomycosis. It will affect on both the toe nails and finger nails. Complications of the disease include skin injury, adjacent to the nail and will allow the organisms to colonize, which will lead to several infectious complications. There are lot of factors that resulted in an increased prevalence of Onychomycosis. These include the wearing of shoes, Trauma, exposure to water, chemical and soil contact etc.
The above mentioned issues motivated us to undertake the present study which is aimed to assess the effectiveness of monotherapy and combination of systemic and topical antifungals.

**KEYWORDS**: Onychomycosis, Distal and lateral subungual onychomycosis, Proximal subungual onychomycosis, Superficial white onychomycosis, Total dystrophic onychomycosis, Candida Onychomycosis

## I. INTRODUCTION

Onychomycosis is a fungal infection of nails. It is caused by dermatophytes, yeasts, and nondermatophytic molds where dermatophytes account for nearly 70% of the cases[1]. Although onychomycosis is not life threatening, the psychosocial and emotional effects of the disease can cause negative impact on the quality of life of those affected[2,3]. Types of Onychomisis include Distal and lateral subungual onychomycosis, Proximal subungual onychomycosis, Superficial white onychomycosis, Total dystrophic onychomycosis and Candida Onychomycosis.

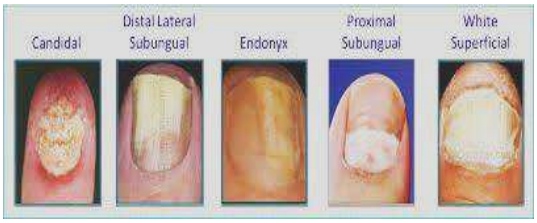


**Figure 1: Types of Onychomycosis.**

The aging of population, increased use of immunosuppressive drugs, an increase in the prevalence of underling disease such as HIV and diabetes that suppress the immunostatus of patients, increased exposure to public swimming pools, the use of tightly fitting shoes for fashions, and long-distance running in athletic games have been recognized as factor for the rise in the onychomycosis [4,5].
Currently, there are three main pharmacological strategies; Oral treatment , Topical treatment, Combination therapy[6].

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

**Table no.1: Treatment of Onychomycosis**

| DRUGS<br><br>**TOPICAL AGENTS** | DOSE AND DOSAGE FORM(widely used) | MECHANISM OF ACTION |
|---|---|---|
| Ciclopirox ( Hydroxypyridones) | Ciclopirox 8% topical solution [Applied daily] | It causes membrane instability towards inside fungal cells and interfering with amino- acid transport across the fungal cell membrane and causes stopping the growth of the nail fungus. |
| Amorolfine ( Morpholine derivative) | Amorolfine 5% w/v nail lacquer Amorolfine cream Amorolfine cream 0.25% w/w | Inhibit ergosterol biosynthesis in the fungal cell membrane and disrupt fungal metabolic process |
| Luliconazole (Azole derivatives) | Luliconazole cream 1% w/w Luliconazole 1%w/v | Inhibit ergosterol synthesis by inhibiting the enzyme lanosteroldemethylase. |
| Efinaconazole (Azole derivative) | Efinaconazole 10% w/w Topical solution | Inhibit fungal lanosterol 14-alpha-demethylase, an enzyme necessary for the biosynthesis of ergosterol |
| Tavaborole (Oxaborole antifungal) | Tavaborole 5% topical solution | Inhibits protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid synthetase |

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

| | | |
|---|---|---|
| **SYSTEMIC AGENTS** | | |
| Terbinafine (allylamines) | Terbinafine 250mg, Terbinafine Hydrochloride cream 1% | Inhibit squalene epoxidase enzyme and kill fungi. |
| Itraconazole (azole derivatives) | Itraconazole 200mg | They inhibit the synthesis of ergosterol by inhibiting lanosterol 14-alpha demethylase |
| Fluconazole (azole derivatives) | Fluconazole 150-300mg | Inhibit the conversion of lanosterol to ergosterol via binding to fungal cytochrome P-450. |

**COMBINATION THERAPY**

· Based on potential drug- drug interactions and systemic side effects of oral agents and the poor-efficacy and time consuming treatment courses of topical drugs, there is a need for alternative and novel therapies[7].

· Combination of both oral and topical antifungals is a beneficial and most effective approach in treating onychomycosis[8].

· The combination of oral and topical drugs may allow reduction in oral dosing resulting in increased patient tolerance and compliance while improving efficacy and reducing relapse[8].

Ciclopirox lacquer combined with Terbinafine and Itraconazole was found to increase the percentage of cured patients[9]

Combination of Itraconazole derivative and Terbinafine are equally effective and safe in the treatment of onychomycosis[10].

· Luliconazole has the advantage of effectiveness even on once daily application, hence can improve compliance and they are combined with Amorolfine, Terbinafine, Itraconazole/ Fluconazole antifungals[10].

## II. MATERIALS AND METHODS

A Prospective-observational study was conducted in 60 patients from inpatient and outpatient Department of Dermatology in a tertiary care hospital who were diagnosed with Onychomycosis and receiving antifungals.

**Inclusion Criteria**

a) Patients at age group of 20-80
b) Patients having history of trauma, diabetic, nail infection who is having onychomycosis

**Exclusion Criteria**

a) Those who were unwilling to give informed consent form.
b) Serious skin disorders or allergies other than onychomycosis.
c) Psychiatric/psychological dysfunction
d) Pregnant, lactating women
e) Hypersensitive to antifungal agent

A written informed consent was taken in prescribed format from the patients diagnosed with Onychomycosis satisfying the inclusion and exclusion criteria. All information relevant to study was collected from case records and direct interview with patients. The demographic details, clinical background (duration of disease, number of drugs being using), drug dose, frequency, etc. was

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

documented in the proforma. The physical examination, degree of severity and KOH method (whenever necessary) were recorded on each visit during study period. The patients were reviewed for follow ups. Outpatients and Inpatients were selected for the study. The patients was divided into two groups, 30 patients receiving monotherapy as Group I and other 30 patients receiving combination therapy as Group II and the KOH method was done on each individual.

A structured interview with patient or care giver was conducted by using questionnaire to get information about their life style and dietary habit. Proper counseling about drugs and disease and about the modification of life style was given to the patients, by using validated Patient Information Leaflet. The counseling was provided at each visit and also the changes within the score were recorded. The outputs were statistically plotted.

The DLQI questionnaire contains 10 questions and scoring range between 0-30, questions were asked to the patients before and after treatment. The scores representing 0 –1 no effect on patient's life, 2 – 5 small effect on patient's life, 6 – 10 moderate effect on patient's life, 11 – 20 very large effect on patient's life, 21 – 30 extremely large effect on patient's life. SCIO scoring was calculated and recorded. SCIO scoring from 1-30, the effectiveness of the treatment was obtained through this scoring method. The SCIO index proved an accurate indicator of therapeutic effectiveness.

## III. STATISTICAL ANALYSIS

All the data were represented as percentage distribution. The association between qualitative study variables was assessed by Chi-square test. A calculated P value <0.05 is considered to be statistically significant. All the analysis were done using SPSS, version 22.0. The effect of patient counseling on DLQI was done using SAS.

## IV. RESULTS

### GENDER DISTRIBUTION

In Group I, out of 30 patients 19 were females (63.3%) and 11 were males (36.7%) and in Group II, the number of females were 20 and males 10. The gender is illustrated in fig.2.

| Gender | Group I | | Group II | | Total | |
|---|---|---|---|---|---|---|
| | n=30 | % | n=30 | % | n=60 | % |
| Female | 19 | 63.3 | 20 | 66.7 | 39 | 65 |
| Male | 11 | 36.7 | 10 | 33.3 | 21 | 35 |
| Total (60) | 30 | 100 | 30 | 100 | 60 | 100 |

**Table 2**: Gender distribution

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

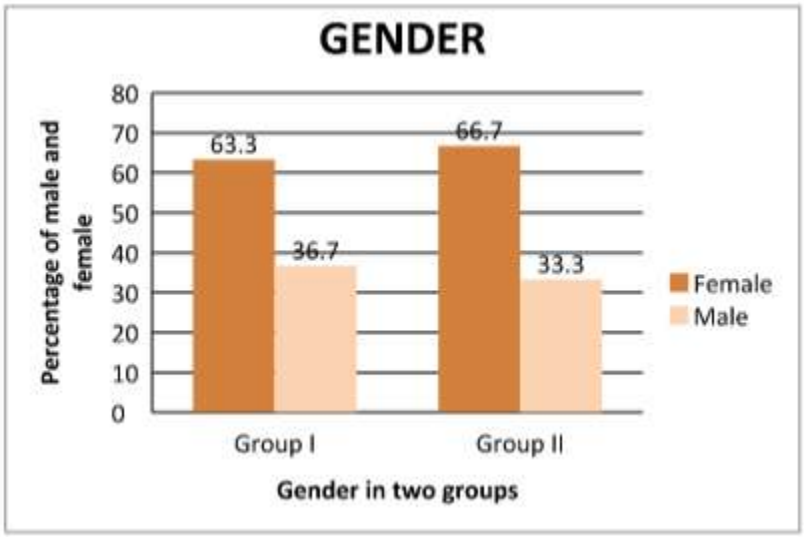


**Figure 2**: Gender distribution in onychomycosis therapy, showing who were more involved in monotherapy and combination therapy. In both Group I and Group II females were more involved

**AGE DISTRIBUTION**

| Age | Group I | | Group II | | Total | |
|---|---|---|---|---|---|---|
| | n=30 | % | n=30 | % | n=60 | % |
| <50 | 8 | 26.7 | 5 | 16.7 | 13 | 21.7 |
| 51-60 | 10 | 33.3 | 10 | 33.3 | 20 | 33.3 |
| 61-70 | 9 | 30 | 11 | 36.7 | 20 | 33.3 |
| >70 | 3 | 10 | 4 | 13.3 | 7 | 11.7 |
| Total | 30 | 100 | 30 | 100 | 60 | 100 |

**Table 3**: Age distribution

Based on the age, the patients were divided into 4 groups. Figure 5 represents the age group classification of onychomycosis patients. It suggests that majority of patients were in the age group of 51-60 in case of monotherapy, ie 10 (33.3%) and least were in the age group of above 70, ie 3 (10%).

In case of combination, majority were seen in the age group of 61-70, ie 11 (36.7%) and least is seen in the age group of above 70, ie 4 (13.3%). From both the age groups, it is specific that at the age of between 50-70 were more prone to onychomycosis.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

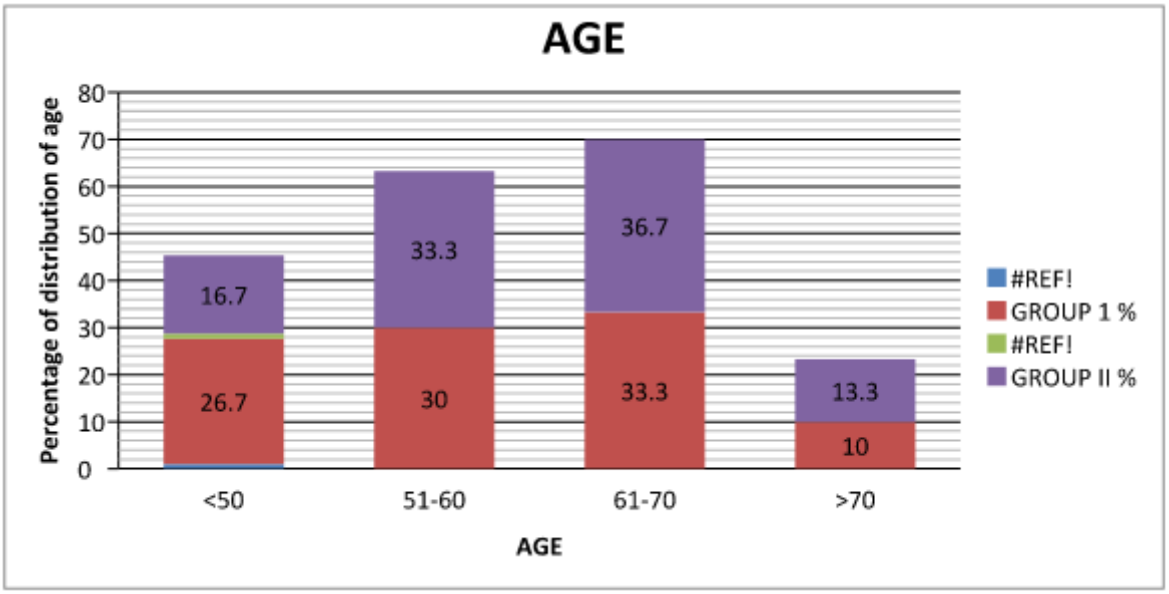


**Figure 3**: Percentage distribution of sample according to age in onychomycosis.

**TYPES OF ONYCHOMYCOSIS**

| Type | Group I | | Group II | | Total | |
|---|---|---|---|---|---|---|
| | n=30 | % | n=30 | % | n=60 | % |
| DLSO | 11 | 36.7 | 27 | 90.0 | 38 | 63.3 |
| PSO | 11 | 36.7 | 3 | 10.0 | 14 | 23.3 |
| SWO | 8 | 26.7 | 0 | 0.0 | 8 | 13.3 |
| Total | 30 | 100.0 | 30 | 100.0 | 60 | 100.0 |

**Table 4**: Types of onychomycosis

The types of onychomycosis are DLSO, PSO and SWO. The percentage distribution of these classes showed that DLSO were more while comparing both the groups, ie 38 (63.3%) and least is SWO, 8(13.3%). In case of monotherapy, majority were seen in both PSO, 11(36.7%) and DLSO, 11(36.7%) and least in SWO, 8(26.7%). In case of combination, majority were in the class of DLSO, 27(90%) and least in SWO.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

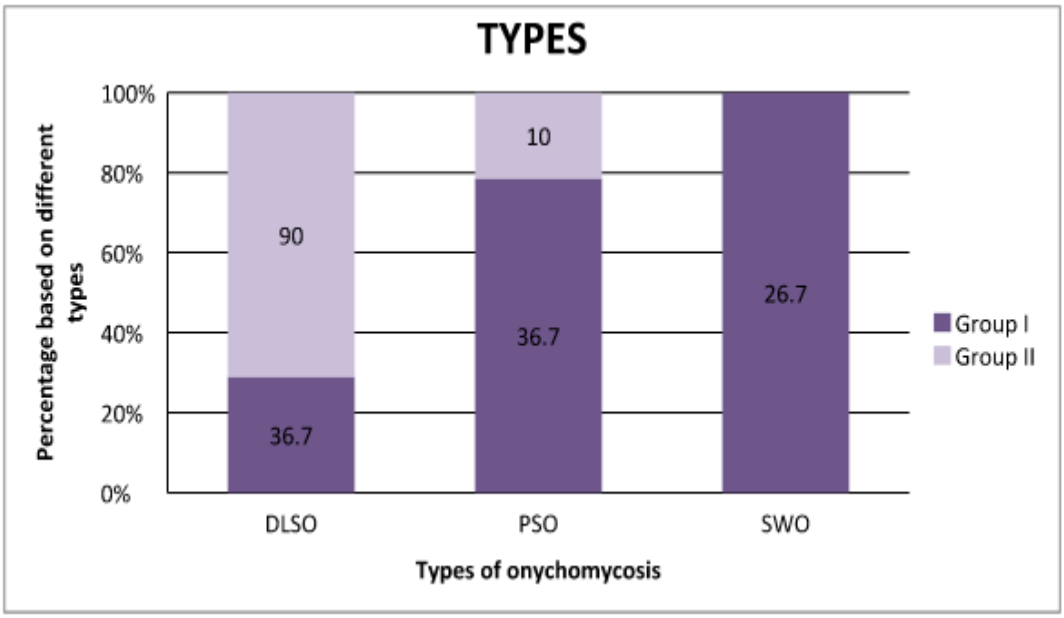


**Figure 4**: Percentage distribution of samples according to different types of onychomycosis.

**AREA OF INVOLVEMENT**

| Area | Group I | | Group II | | Total | |
|---|---|---|---|---|---|---|
| | n=30 | % | n=30 | % | n=60 | % |
| Finger nails | 13 | 43.3 | 9 | 30.0 | 22 | 36.7 |
| Toe nails | 14 | 46.7 | 17 | 56.7 | 31 | 51.7 |
| Finger nails and Toe nails | 3 | 10.0 | 4 | 13.3 | 7 | 11.7 |
| Total | 30 | 100.0 | 30 | 100.0 | 60 | 100.0 |

**Table 5**: Percentage distribution of samples according to area of involvement.

Onychomycosis can affect either finger nails/toe nails/both the nails. Figure 5 describes the percentage of area of involvement of nails. In case of monotherapy 14(46.7%) patients are reported for toe nail infection and 13(43.3%) for finger nails. While in combination, 17(56.7%) were having infected toe nails and 9(30%) patients having infected fingernails. By comparing both the groups, majority of cases were reported for toe nail infections, 31(51.7%) than finger nails, 22(36.7%).

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

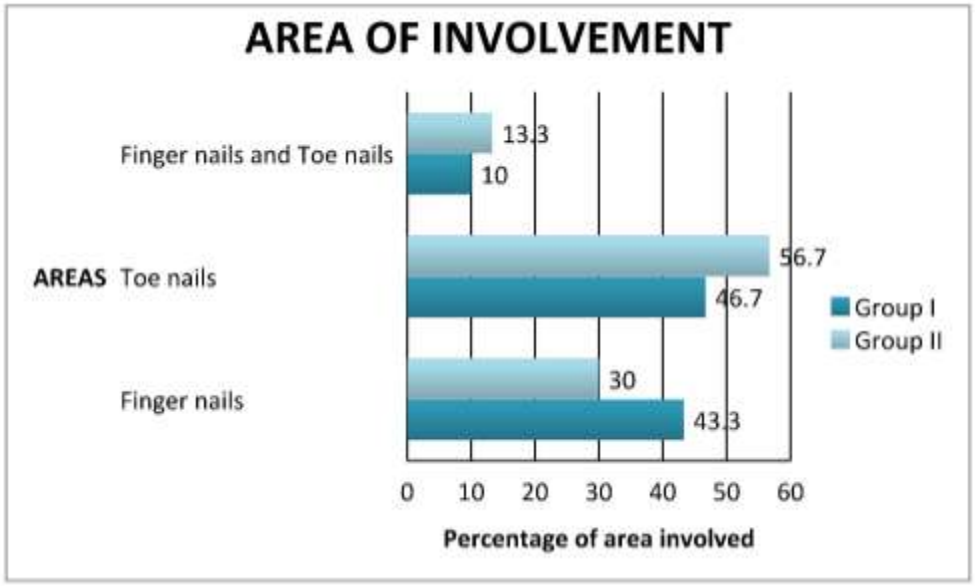


**Figure 5**: Percentage distribution of samples according to area of involvement.

**ASSESSMENT OF BETTER THERAPY**

**DESCRIPTIVE STATISTICS OF SCIO INDEX**

| Group I | n | SCIO score | | Paired t test | |
|---|---|---|---|---|---|
| | | mean | sd | t | p |
| Before treatment | 30 | 5.46 | 4.09 | 3.18 | 0.003 |
| After treatment | 30 | 4.03 | 2.33 | | |
| Group II | n | SCIO score | | Paired t test | |
| | | mean | sd | t | p |
| Before treatment | 30 | 17.49 | 4.26 | 21.164 | <0.001 |
| After treatment | 30 | 6.76 | 2.81 | | |

**Table 6:** The statistical values of SCIO index of samples in Group I & II before and after treatment.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

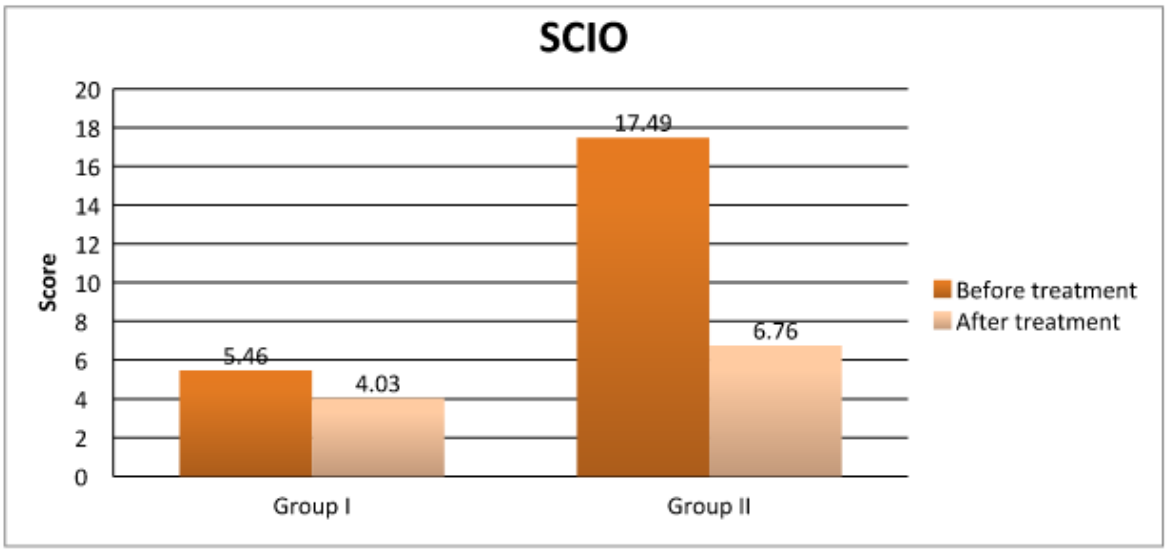


**Figure 6:** The mean of SCIO Index in samples before and after treatment.

From the figure it is clear about the clinical response of the patients towards the therapy. SCIO give an index of the overall severity of onychomycosis and it may be possible to better compare the clinical response to therapy. The higher score (range is 1 -30) suggests that the condition is more severe and may require more prolonged treatment. In case of group II, there is a mean difference of 10.73 between before and after treatment and in group I, the mean difference is 1.43, showing minor variation in the score. From the data it is clear that combination therapy is more effective than monotherapy.

**ONYCHOMYCOSIS TREATMENT DETAIL**

| **GROUP-1** | DRUGS USED IN MONOTHERAPY | | | | | |
|---|---|---|---|---|---|---|
| | LULICONAZOLE | CICLOPIROX | AMOROLFINE | FLUCONAZOLE | ITRACONAZOLE | TOTAL |
| **n** | **17** | **5** | **4** | **2** | **2** | **30** |
| **Percentage (%)** | **56.67** | **16.67** | **13.33** | **6.66** | **6.66** | **100** |

**Table 7**: Percentage distribution of drugs used in the monotherapy

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

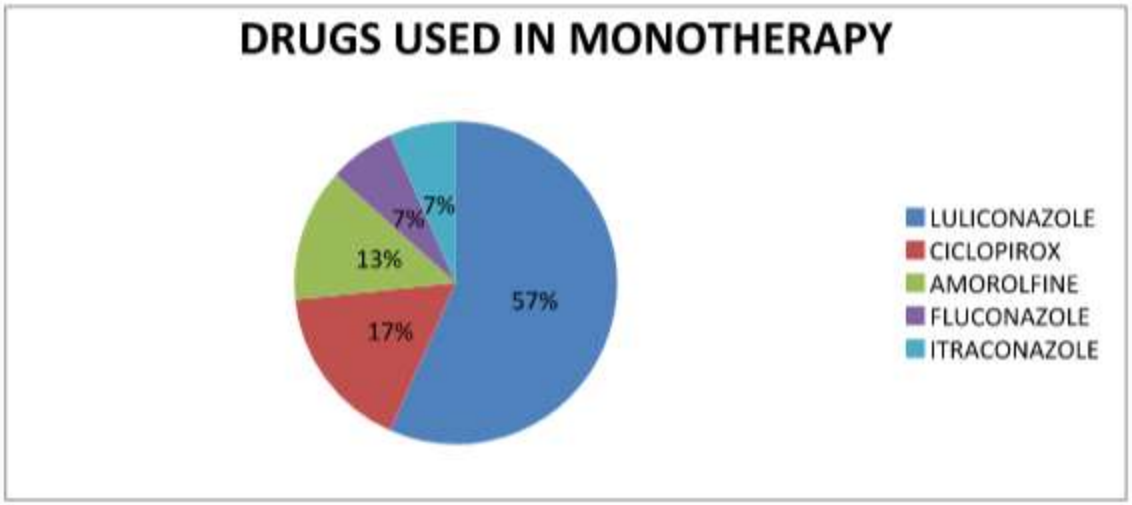


**Figure 7**: Percentage distribution of drugs used in the monotherapy. From the figure it is clear about the drugs used in the monotherapy, it shows that the luliconazole was most effective in case of monotherapy.

| **GROUP- 2** | **DRUGS USED IN COMBINATION THERAPY** | | | | | | |
|---|---|---|---|---|---|---|---|
| | LULICONAZOLE & FLUCONAZOLE | LULICONAZOLE & ITRACONAZOLE | FLUCONAZOLE & AMOROLFINE | ITRACONAZOLE & AMOROLFINE | FLUCONAZOLE & CICLOPIROX | ITRACONAZOLE & CICLOPIROX | TOTAL |
| n | 15 | 5 | 4 | 3 | 2 | 1 | 30 |
| PERCENTAGE (%) | 50 | 16.67 | 13.33 | 10 | 6.66 | 6.66 | 100 |

**Table 8**: Percentage distribution of drugs used in the combination therapy.

**Figure 8**: Percentage distribution of drugs used in the combination therapy. From the figure it is clear about the drugs used in the combination therapy, it shows that the luliconazole and fluconazole were most effective in case of combination therapy.

## V. DISCUSSION

Onychomycosis is a fungal infection affecting the nails of both finger and toe. The nails become white and opaque, thickened and brittle. Treatment mainly includes oral antifungals like Terbinafine, Itraconazole, Fluconazole and topical antifungals includes Amorolfine, Ciclopirox, Luliconazole, Efinaconazole etc. Based on the severity the type of the treatment get varied ie, monotherapy and combination therapy.

Although this disease is not a life-threatening, it may cause significant clinical consequences such as secondary bacterial infections, chronicity, therapeutic difficulties, and disfigurement apart from serving as a reservoir of infection. The patients having onychomycosis along with diabetes increases the risk for other foot disorders and trigger for more severe complications such as foot ulcers, gangrene, recurrent cellulitis and limb amputation.

Factors such as ageing, immunodeficiency, trauma, hyperhidrosis, socioeconomic status, climatic conditions, and paronychia predispose to onychomycosis. The duration of therapy depends on the nails that are affected and the extent of infection. Affected fingernails require 3 months of therapy and toenails need 6 months. Based on the severity it was given 1-3 months, the microscopy was negative after 2 months, if the discoloration of the nails failed to improve indicating that there might be a persistent reservoir of infection, in such situations the therapy continues.

In our study, we have evaluated the effectiveness of combination therapy and monotherapy in the treatment of onychomycosis after clear analysis of the medical records of the

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 1667-1678 www.ijprajournal.com ISSN: 2249-7781

patients. Data on personal details of 60 patients regarding the family history of disease, current evidence of disease were all collected. We divided the total patients into two groups based on their treatment ie, Group I (30) shows monotherapy and Group II (30) shows combination therapy which was supported by a study done by Hera Tabassum et al[48].

In our study female patients were more common, in case of Group I, out of 30 patients 19 were females (63.3%) and 11 were males (36.7%) and in Group II, the number of females were 20 and males 10. This result was supported by a study done by Adane Bitew and shows that more female subjects were more likely to present for nail dystrophy than male patients[11].

Based on our inclusion criteria, age group of 20-80 was again categorized into 4 groups of [<50], [51-60], [61-70] and [>70]. By our study we found that at the age group of 51-60 were more prone to onychomycosis in monotherapy ie, 10 (33.3%) followed by the age group of 61-70 and in case of combination therapy 61-70 (30%) age groups ie, 11 (36.7%) followed by the age group of 51-60 (33.3%) and was supported by a study done by Dr. Archana singal et al. Similar to our study, elderly patients were more affected due to increased incidence of onychomycosis and poor treatment response with age are attributable to risk factors such as poor peripheral circulation, repeated trauma, suboptimal immune function, and inability to maintain good foot care[12].

Onychomycosis is further classified based on different types – DLSO, PSO and SWO. In case of group 1 shows both DLSO and PSO types were more ie, (36.7%) followed by SWO (26.7%) and in combination majority was in DLSO ie, (90%) followed by PSO(10%).The percentage distribution of different classes showed that DLSO were more while comparing both the groups, ie 38 (63.3%). In the study of Mustafa Gulgun DLSO type could be seen in children and adults. While assessing severity of onychomycosis, monotherapy shows mild cases,ie 22(73.3%) followed by moderate cases, ie 7(23.3%) and in case of combination therapy severe cases were more ie, 21(70%) followed by moderate cases 9(30%).

Toenails are more likely to be infected than finger nails because ofthe causative molds like fungi seen in soil, water, and decaying vegetation's. By comparing both the groups, we found that majority were reported for toe nail infection ie, 31 (51.7%).In our study, the patients having risk factors like diabetic, trauma, infections, water contact and others were included; from these risk factors we found that diabetic patients (63.33%) were more prone to onychomycosis, followed by water contact and trauma (51.67%) and least in others ie, 8.3%.Our result was supported by a study done by Mudita gupta showing toe nails were more affected than the finger nails. The prevalence of onychomycosis has been shown to be significantly higher in diabetic patients than normal individuals was supported by a study done by Sarma .S et al[13].

In our study different drugs were used in the treatment of onychomycosis, for monotherapy– Luliconazole, Amorolfine, Ciclopirox, Fluconazole and Itraconazole, out of those Luliconazole were widely prescribed for monotherapy, ie 17 patients (56.67%), it is because of availability and decrease in adverse reactions. In case of combination therapy, combination of Luliconazole (1%w/v) and Fluconazole (150mg) were prescribed more. Co-administration of oral and topical agent enhances the number of patients cured and they have dose sparing effect.

SCIO give an index of the overall severity of onychomycosis and it may be possible to better compare the clinical response to therapy. The higher score (range is 1 -30) suggests that the condition is more severe and may require more prolonged treatment. In our study we conducted SCIO index scoring, before starting treatment and re assessed after 2 weeks during review. In case of group II, there is a mean difference of 10.73 between before and after treatment and in group I, the mean difference is 1.43, showing minor variation in the score. By this we concluded that combination therapy were most effective than monotherapy from paired t test.

## VI. CONCLUSION

In summary we concluded that combination therapy is more effective than monotherapy. Co-administration of oral therapy with a topical agent can result in dose- sparing effects and can increase the number of patients cured rather than monotherapy. In addition, cost savings can be made by using combination therapy.

Although several topical and oral agents were prescribed for the treatment of onychomycosis. In the present study Luliconazole (topical agent) were more prescribed as monotherapy and combination of Luliconazole and Fluconazole were seen in combination therapy. Here the Luliconazole is prescribed because of

their availability and mild application site reaction. Fluconazole (150mg) have rapid penetration in to the nail bed. A rapid decrease in the scoring of SCIO indicates that combination therapy is more effective.

## REFERENCE

[1]. Sageerabanoo, Malini A, Oudeacoumar P, Udayashankar C. Onychomycosis due to Trichosporonmucoides. Indian J DermatolVenereolLeprol 2011;77:767
[2]. Fouilloux B. Onychomycosis and quality of life. Ann DermatolVenerol 2003;130:1257-8.
[3]. Lubeck DP. Measuring health-related quality of life in onychomycosis. J Am AcadDermatol 1998;38:S64-8.
[4]. S. M. Hwang, M. K. Suh, and G. Y. Ha, "Onychomycosis due tonondermatophytic molds," Annals of Dermatology, vol. 24, no. 2, pp. 175–180, 2012.
[5]. 6. G. Moreno and R. Arenas, "Other fungi causing onychomycosis," Clinics in Dermatology, vol. 28, no. 2, pp. 160–163, 2010.
[6]. Katarzyna Tabara, Anna E. Szewczyk et al. Amorolfine VS. ciclopirox – lacquers for the treatment of onychomycosis. PostepDermAlergol 2015; 1: 40-45.
[7]. Shari R Lipner et al. Efinaconazole in the treatment of onychomycosis. Infection and drug resistance 2015;8:163-172
[8]. ArchanaSingal et al.Onychomycosis: Diagnosis and management.ijdvl 2011;vol 7: issue 6: 659-672
[9]. Bhatt v, Sarpotdar P, Pillai r, et al. Development of an optimal formulation for efinaconazole a novel antifungal agent for the treatment of onychomycosis by topical application. Poster presented at 71st Annual Meeting, American Academy of Dermatology; Miami Beach FL; 2013.
[10]. Sigurgeirsson B, Olafsson JH, Steinsson JT, et al. Efficacy ofamorolfine nail lacquer for the prophylaxis of onychomycosis over 3 years. J EurAcadDermatolVenereol 2010; 24:910-5.
[11]. Hera Tabassumet et al. The impact of onychopathies on quality of life: a hospital-based, cross-sectional study.(2019).
[12]. Kaur R, Kashyap B, Bhalla P. Onychomycosis-epidemiology, diagnosis and management. Indian J Med Microbiol 2008;26:108-16.
[13]. Mustafa Gulgun. Prevalence and risk factors of onychomycosis in primary school children living in rural and urban areas in Central Anatolia of Turkey. ijdvl. 79(6):777-82;2013.