A SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF PHOTOTHERAPY TREATMENTS WITH SEBORRHEIC DERMATITS

BY

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Abstract

Seborrheic dermatitis is one of the most common chronic inflammatory skin diseases. The etiology of seborrheic dermatitis is unclear; however, some studies suggest that both a vulnerable immune system and the invasion of yeasts on the patient's skin could contribute to the condition. To treat seborrheic dermatitis, there are many modulators divided to local treatments and systemic treatments. Using the ultraviolet to ease symptom is one of the alternative treatments. However, the systematic review of the effectiveness of ultraviolet treatment is not yet clarified yet. This study aims to investigate the effectiveness of phototherapy treatments for seborrheic dermatitis. The systematic review is used to categorize the extensive information and perform critical appraisals to assess the quality of the papers. Each study is individually evaluated using the GRADE approach. Additionally, the PRISMA checklist 2020 and the Cochrane Public Health Group Data Extraction and Assessment are employed to clarify study details.

A thorough search initially identified 65 records. After removing duplicates and carefully filtering and evaluating full-text articles, three papers were included in this systematic review: two prospective single-arm trials and one randomized trial with three arms. Each study employed different light therapy types, including green diode light therapy, narrow-band UVB, and intense pulsed light therapy. The heterogeneity of these interventions and research designs made an additional meta-analysis impractical. However, the findings indicate that phototherapy methods such as photodynamic laser, intense pulsed light (IPL) with 30% supramolecular salicylic acid, and narrow-band ultraviolet B (TL-01) phototherapy can offer successful treatment.

Although initial evidence suggests the effectiveness of phototherapy treatments, they should be considered as part of a comprehensive treatment strategy that includes alternative agents. However, the current evidence is limited in both quantity and quality. Therefore, a large-scale randomized controlled trial is needed to establish the efficacy of phototherapy in treating seborrheic dermatitis.

(Total 45 pages)

Keywords: Seborrheic dermatitis, Phototherapy, Dermatitis, Ultraviolet

Student's Signature …..... Thesis Advisor's Signature .....

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Abbreviations and Symbols

Symbol	Meaning
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
UV	Ultraviolet
UVB	Ultraviolet B
UVA	Ultraviolet A
SD	Standard Deviation
PUVA	Psoralen Ultraviolet A
NBUVB	Narrowband Ultraviolet B
BBUVB	Broadband Ultraviolet

Chapter 1

Introduction

1.1 Background and significance of the problem

Seborrheic dermatitis is one of the most common chronic inflammatory skin diseases which we can find in any ethnicity, especially with HIV infection and AIDs. Sometimes, the patients who are diagnosed with seborrheic dermatitis have the issue of taking oral medication either the medications can not ease the symptoms so they might desperately need other options.

Nowadays, there is an update of seborrheic dermatitis according to evidence-based medicines. So, we can decide what is the best treatments for the patients. However, there are many optional treatments that we use to treat the disease, having used Ultraviolet is the choice that we still unclearly know about its effectiveness. However, there is a comprehensive review of the treatments of seborrheic dermatitis, phototherapy is not yet studied systematically.

1.2 Research objectives

1.2.1 In order to being understand the effective of the phototherapy for treating seborrheic dermatitis which is uncertainly known about its risks and benefits.

1.2.2 To update the knowledge about the selective ultraviolet treatments for seborrheic dermatitis which are not reviewed systematically yet.

1.2.3 Regarding the updated knowledge about ultraviolet treatment, we can manage to make the proper remedy for the patients.

1.3 Research questions/assumptions

The effectiveness of phototherapy with seborrheic dermatitis

1.4 Research framework

1st year

Table 1.1 1st year

Plan	2022											
	Oct.	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**
1. research question	---B	000										
2. written proposal			000	000								
3. present proposal					000							
4. collect the data						000	000	000				

2nd year

Table 1.2 2nd year

Plan	2023											
	Oct.	**Nov**	**Dec**	**Jan**	**Feb**	**Mar**	**Apr**	**May**	**Jun**	**Jul**	**Aug**	**Sep**
5. Data analysis	000	000										
6.written manuscript			000	000	000							

1.5 Definition of terms

Systematic review - A review that uses explicit, systematic methods to collate and synthesize findings of studies that address a formulated question (Higgins et al., 2019)

Statistical synthesis - The combination of quantitative results of two or more studies. This encompasses meta-analysis of effect estimates (described below) and other methods, such as combining P values, calculating the range and distribution of observed effects, and vote counting based on the direction of effect. (McKenzie & Brennan, 2019)

Meta-analysis of effect estimates - A statistical technique used to synthesize results when study effect estimates and their variances are available, yielding a quantitative summary of results (McKenzie & Brennan, 2019)

Outcome - An event or measurement collected for participants in a study (such as quality of life, mortality)

Result - The combination of a point estimate (such as a mean difference, risk ratio, or proportion) and a measure of its precision (such as a confidence/credible interval) for a particular outcome

Report - A document (paper or electronic) supplying information about a particular study. It could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report, or any other document providing relevant information

Record - The title or abstract (or both) of a report indexed in a database or website (such as a title or abstract for an article indexed in Medline). Records that refer to the same report (such as the same journal article) are “duplicates”; however, records that refer to reports that are merely similar (such as a similar abstract submitted to two different conferences) should be considered unique.

Study - An investigation, such as a clinical trial, that includes a defined group of participants and one or more interventions and outcomes. A “study” might have multiple reports. For example, reports could include the protocol, statistical analysis plan, baseline characteristics, results for the primary outcome, results for harms, results for secondary outcomes, and results for the additional mediator and moderator analyses

UVB - ultraviolet B

UVA - Ultraviolet A

Chapter 2

Literature Review

According to the term of the research question, seborrheic dermatitis is a chronic inflammatory skin disease which we are willing to study systematically about the effectiveness of narrowband UVB in order to treat the disease.

2.1 Seborrheic dermatitis

Seborrheic dermatitis is the chronic inflammatory skin disease which is categorized to papulosquamous dermatosis. Seborrheic dermatitis can be found in any ethnics and age groups. The patients are presented with the desquamation of skin and sign of inflammation, including macules or papules. The seborrheic areas are the pathological sites that are located at the face, chest and scalp. There is the study mentions that the disease also can cause psychosocial effects and decrease the quality of life of the patients (Xuan, Lu, & He, 2020).

2.1.1 Incidence

Seborrheic dermatitis can be found at either any age or ethnicity. However, newborns are a higher prevalence than adults as well as boys is higher risk than girls (Foley, Zuo, Plunkett, Merlin, & Marks, 2003).

Especially, patients who are diagnosed with acquired immunodeficiency syndrome increase the risk of having the disease by about 85% (Basset-Séguin, Sotto, Guillot, Jourdan, & Guilhou, 1998) as well as Parkinson's disease, increases the risk of having seborrheic dermatitis (Gregory & Miller, 2015)

2.1.2 Etiology and pathogenesis

Seborrheic dermatitis (SD) is one of the most common dermatological diseases and there is a high prevalence Even though, the etiology is rarely known. There are several factors such as Malassezia yeasts, hormones, sebum levels, immune response, neurogenic factors, and external factors that seem to be related to SD, but the exact pathogenetic mechanism still remains controversial.

2.1.2.1 the pathological at the sebaceous unit on the skin

1) Seborrhea is the sign of oily skin, having the pathology over the sebaceous area which is cause by the androgen especially the newborn has the huge sebaceous gland. As a result of the effect of the maternal androgen pass through the newborn, the lesion likely to be appeared in the 1st 3 moths and improve when the androgen is decreased. Also, Adulthood will be affected by androgen again (Hegge, Boon, & Verheij, 2006).

2) abnormalities of lipid compositions, the research found that the lipid level is not related to the severity of the disease. On the other hand, the compositions of lipids such as cholesterol triglycerides paraffin squalene free fatty acids are increased in the ratio but the wax esters ratio is decreased. So, the keratin synthesis would be disturbance (Plewig & Jansen, 2008).

2.1.2.2 Malassezia species

Malassezia is the dimorphic fungi, lipophilic yeast form is the normal form of the normal flora on the skin. The number of Malassezia is increased in Seborrheic dermatitis patients (McGinlley, Leyden, & Marples, 1975) as well as the dandruff has shown of increasing the number of yeasts which we believe that Malassezia is the cause (Korting, Schaller, Altmeyer, Braun-Falco, & Ruppert 2002).

As a result of the evidence indicates that Malassezia spp. is the factor in SD. After treatments with the antifungal,the lesion is improved . This is shown that Malassezia spp. have an important role in the development of SD. Malassezia spp. are lipophilic yeasts that are ubiquitous residents of the skin (Gupta, Batra, Bluhm, Boekhout, & Dawson, 2004). They are predominantly situated on lipid-rich anatomic areas.

Regarding the recent study, we believe that Malassezia spp is one of the cause of SD (Schwartz, Janusz, & Janniger, 2017). However there are some evidences have shown that not only the yeasts itself also the inflammation process due to the metabolite of epidermis can cause of T cell lymphocyte and Langerhans cells are activation (Sohnle & Collins-Lech, 1983). Additionally, The immunocompromised hosts especially Cell mediated immunity incompetence will be vulnerable to protect against the yeast (Victor, Olga, & Zoilo, 1997; Blanco & Garcia, 2008).

2.1.2.3 Neurotransmitter abnormalities

Regarding of the seborrheic dermatitis prevalence, the incidence rate is increasing in some CNS disease such as epilepsy, cerebrovascular disease , spinal cord injury (Robert, Christopher, & Camila, 2006) especially Parkinson disease. The decrease of amount of dopamine in Parkinson ds can cause of hormone disturbance and increase of lipid production which is the cause of inflammation (Mastrolonardo, 2003) along with the study of improvement of the disese after giving L dopa (Potter & Wyburn-Mason, 1970)

2.1.2.4 Immune system

Seborrheic dermatitis is the most common skin disease in HIV infected patients as well as it presents with AIDs patients which is severe (Berger, Stoner, Hobbs, Hayes, & Boswell, 1998). So, the treatments of seborrheic dermatitis with immunocompromised host are reluctant and the disease are severe.

2.1.2.5 emotional

Stressed and emotional disturbance can cause of SD because the lipid production will be inclined over the sebaceous area (Ender, Cosar, Eztar, & Candansayar, 2005) even though the pathological mechanism is unclear.

2.1.2.6 Drugs

There are many reports found that some medication can cause of seborrheic dermatitis such as arsenic gold methyldopa cimetidine neuroleptic drugs (Plewig & Jansen, 2008).

2.1.2.7 Climate

Weather and climate are also known to affect seborrheic dermatitis. In countries with temperate climate and four seasons, seborrheic dermatitis generally worsens in the winter and autumn, and improves in the summer (Mohamed, Cheong, Ng, & Tan, 2014). These changes are believed to be caused by low sun exposure, which is a risk factor of seborrheic dermatitis (Goldberg, Kircik, Friedlander, & Maibach, 2013). On the contrary, several studies reported sun exposure as a non-microbial factor which causes dandruff and exacerbation of seborrheic dermatitis (Cheong, Mohamed, Ng, & Tan, 2016).

Ultraviolet radiation is thought to cause hyperplasia of sebaceous glands and changes in the skin surface's lipid composition, leading to disturbances in skin's defenses (Akitomo, Fujimoto, Nishimura, & Tokura, 2017). Thus, the role of sunlight in the pathogenesis of seborrheic dermatitis is controversial.

2.1.3 Clinical finding

In order to draw the treatment plans we need to categorized the clinical finding which we have been using the age of the patient.

2.1.3.1 Newborn

Three months after birth is the most common age of having SD. we can see the lesion over the scalp and skin crease which is scaly and oily. If the lesion seems more thick scale and flaky which we call cradle cap. Also, if the rash come along to the ear lobes we might need to aware of external otitis.

The prognosis is good, there is the self-limitation at 6 months old due to the decreasing of the maternal hormone.

In some newborn who have the severe symptom (erythroderma) with diarrhea or vomiting, the evidence of immunodeficiency needs to be investigated.

2.1.3.2 Adulthood

Regarding the presentation of the disease, the symptom is different to the newborn. So, we can categorize regard to the severities

1) Seborrheic eczematoid, Pityriasis sicca, and Erythema paranasal

1.1) Seborrheic eczematoid is the mild severities of seborrheic dermatitis which we can see the erythematous rash with scale and oily skin. So, we can find this lesion at scalp, eye browns, nasolabial fold, ear lobe, chest and back.

1.2) Pityriasis sicca is the white scale on scalp which we call dandruff

1.3) Erythema paranasal is the erythematous patch over the nasolabial fold, being found in female more than male.

2) Patchy seborrheic dermatitis is the most common symptom in chronic seborrheic dermatitis.

3) Seborrheic erythroderma is the most severe type seborrheic dermatitis

2.1.4 Histology

2.1.4.1 Acute and subacute stage

In this phase we can see lymphocytes and histiocytes are surrounding the capillary in the superficial dermis. Spongiosis and orthokeratosis are presented as well as the neutrophils accumulate over the pore of hair follicles.

2.1.4.2 Chronic stage

We can see the dilatation of capillary and small venules which we call this pattern as Psoriasiform pattern. So, it difficult to distinguish between psoriasis and seborrheic dermatitis.

2.1.5 The diagnosis of Seborrheic dermatitis

Seborrheic dermatitis can be diagnosed with the clinical symptoms, having the investigation is not necessary (Aditya, Madzia, & Roma, 2004). However, the skin biopsy can be done if the clinical is unable to distinguish between psoriasis. Additionally, fugal cultured is suggested when the lesion is likely Tinea capitis. (Shutter, 1984).

2.1.6 Treatments

2.1.6.1 Corticosteroids

The effect of antiinflammation of the steroid has the good outcome however SD is the chronic disease and facial lesions are most common. So, the potency of the steroid is recommended regarding the site of lesion (Abramovitis & Perlmutter,

2006) for example scalp is able to use moderate potency and face need to use mild potency of steroid in order to avoid the side effects.

2.1.6.2 Antifungals

Regarding of the study (Abramovits & Perlmutter, 2006) 4 weeks after using the antifungal drugs, imidazole group, about 62 % of patients have improved. Ketoconazole is the most common used drug. Additionally, the study found that in the ketoconazole used group has longer time of remission compare to the steroid used group (Katsambas, Stefanaki, & Panagiotidou, 1989). Moreover, the study shown that ciclopirox cream has the higher effect than the placebo (Dupuy, Maurette, & Amoric, 2001) and the effect is equal to ketoconazole (Ratnavel, Squire, & Boorman, 2007).

2.1.6.3 Metronidazole gel

The one study found that the effective of metronidazole gel compare to the placebo group are superior significantly (Parsad, Pandhi, Negi, & Kumar, 2001).

2.1.6.4 Lithium succinitate.

8% Lithium succiniatate or 8% lithium gluconate is one of the choices to treat SD effectively (Boyle, Burton, & Faergemann, 1986).

2.1.6.5 Isotretinoin

According to the study found that oral isotretinoin has the effect of decreasing the sebum and antiinflammation (Orfanos & Zouboulis, 1998). So it can use to treat SD. Also, 5-10 mg/day can prevent the relapse however we only prescribe to sever cases and reluctant to the other treatments because the side effects (Bowszyc, 1998).

2.1.6.6 Immunomodulators

Tacrolimus and pimercrolimus are being used to treat SD as a result of antiinflammation effects and some study found that it can fight against M.fur fur in vitro (Ling, 2001).

2.1.6.7 Phototherapy

The use of ultraviolet (UV) light as a treatment for inflammatory dermatoses was firstly studied in 1903 by Dr. Niels Finsen, and later in 1925 by Goeckerman. UV phototherapy uses a selective range of UV light, which can be categorized into ultraviolet A (UVA), psoralen ultraviolet A (PUVA), and ultraviolet B (UVB) irradiation ranges. The UVB category of phototherapy includes broadband UVB (BB-UVB) at 280-320 nm and narrowband UVB (NB-UVB) at 311-313 nm.

The selective of ultraviolet (narrow-band UVB) is being used with the severe cases as well as the failed treatment of the others (Pirkhammer et al., 2000). Also, In sever case such as SD erythroderma type can use the psoralen ultraviolet type A (PUVA) (Dahl & Reymann, 1977).

2.2 Ultraviolet B (UVB)

Most of the seborrheic dermatitis patients are improved in summer. There is the study found that the effect of UVA and UVB light can inhibit on Malassezia yeasts cultured from the skin has been experimentally proved (Pirkhammer et al., 2000). Regarding the prospective study, 18 patients with severe seborrheic dermatitis were treated with narrow-band UVB 3 times per week until clearance or upon completing 2 months of therapy (Ranki, Puska, Mattinen, & Valle, 1991). The median number of treatment sessions was 23 and the median cumulative UVB dose was 9.8 J/cm-2. All patients responded well to therapy, especially those with widespread disease. The major limitations of UVB irradiation for seborrheic dermatitis are the frequent visits to a

phototherapy unit, the rapid disease relapse appearing 2-6 weeks after treatment, and the risks associated with exceeding the maximum lifetime allowable cumulative dose.

2.3 Narrow band UVB (NB-UVB)

Narrowband UVB is the widely used form of phototherapy to treat skin diseases. "Narrowband" refers to a specific wavelength of ultraviolet (UV) radiation, 311 to 312 nm. Also, the NB UVB has shown the fewer effects compare to the others (Sapam & Agrawal, 2012).

Regarding to an inflammatory skin disease, NB-UVB has an effect to a decrease in pro-inflammatory cytokines, a decrease in antigen presentation through inhibition of Langerhans cell activity, and a cascade of biological events which result in suppression of the cutaneous T-cell-mediated immune system.

In term of having used narrowband UVB, NB-UVB has proven to be the particular treatment option for conditions such as vitiligo, psoriasis, mycosis fungoides, atopic dermatitis, pruritus, photo dermatoses, and other skin conditions. It can be used as monotherapy or in combination with topical or systemic agents. Despite its rise in popularity, in the era of the coronavirus disease 2019 pandemic, there was an initial decline in office-based NB-UVB treatments due to concerns of increased viral exposure (Fisher & Ziv, 2020).

2.4 Psoralen plus Ultraviolet A (PUVA)

There is the study, 5 HIV patients who were treated with PUVA treatment (30 to 262 J/cm2 every 2-4 weeks) exhibited clearance of skin lesions, including seborrheic dermatitis (Tegner, 1983). This finding contradicts the report of 28 new cases of facial seborrheic dermatitis appearing during PUVA therapy in 347 patients with psoriasis (Vena, Foti, Grandolfo, Cassano, & Girolomoni, 2005).

2.5 Side effects and risks

Some studies have discussed about having the side effects and risks after using the UV ray either short term or long term. In term of acute complications, we have been awareness of having erythema, burning pain, swelling, and blistering. Also, reactive of herpes simplex virus might happen over the lip which is common in the patients who used to have the prior diagnosis. Chronic complications of UVB therapy include photoaging that clinically appears as leathery appearance, xerosis, wrinkling, pigmentary changes, loss of elasticity, and increased fragility. Especially, some studies show that being exposed to high amounts of artificial UV light raised the risk of skin cancer (Narayanan, Saladi, & Fox, 2010). Also, PUVA may increase skin cancer risks, while narrowband UVB treatment poses no extra skin cancer risk (Lin & Chen, 2009). Phototherapy also can decrease the function of immunities. So, some patients who has been treated for long time which is leaving your body more open to diseases, infections, and skin cancers (Legat, 2018).

So we have to be concerned about risks and benefits of having used ultraviolet light therapy regarding the seborrheic dermatitis which is the chronic disease.

2.6 Contraindications

To minimized the risks of complication, we need to consider about the contraindication (table 2.1).

Table 2.1 The contraindication and relative contraindication for having used ultraviolet treatment

Absolute Contraindications (Juarez & Grossberg, 2020)
Dysplastic naevus syndrome
Systemic lupus erythematosus
Dermatomyositis
Genetic skin cancer syndromes (xeroderma pigmentosum, Gorlin syndrome)

Table 2.1 The contraindication and relative contraindication for having used ultraviolet treatment (Cont.)

Bloom syndrome, Cockayne syndrome
Patients unwilling or unable to comply with safety procedures
Patients who are medically unfit and unable to stand, e.g. severe cardiovascular or respiratory disease
Relative Contraindications
History of exposure to arsenic / ionizing radiation
Previous melanoma
Pregnancy
Current pre-malignant skin condition
Concomitant immunosuppressive therapy
Photo-induced epilepsy
Cataracts
Bullous pemphigoid/pemphigus
Non-melanoma skin cancer
Significant liver dysfunction
Age <16 years

Chapter 3

Research Methodology

Regarding the updated guideline of seborrheic dermatitis which is being used nowadays has not updated about phototherapy yet. So, I would like to do the systematic review by doing the research from the online database within Thai and English since 2000 to present.

The reason to do systematic review

Systematic review is being used to categorized the large amount of information as well as in order to do the critical appraisal which is useful for determine the quality of the papers. Moreover, we can use the analyzed information to build the clinical practice guidelines which is saving time and cost. Systematic review also is able to show the consistency of the results with each paper when we have the large amount of information and we can narrow the confidence interval to build up the accuracy of the information.

Methodology

3.1 Criteria for considering studies

The studies are being selected regard to the retrospective studies which is about the effectiveness of ultraviolet therapy within seborrheic dermatitis.

PICO is the strategy which is used to build the research question. Regarding the study, the research problem is

P: seborrheic dermatitis patients

I: phototherapy

C: the group is not treated with ultraviolet therapy

O: the effectiveness

Search Terms: Used combinations like "*phototherapy OR ultraviolet AND seborrheic dermatitis.*"

3.2 Data collection

We will collect all the studies form the confidential online resources which all the researcher are individually working. Regarding the criteria of selection, if the researcher has the different opinion, the third person including the researcher themselves will find the consensus together.

The data will be collected from PUBMED, Cochrane library, Medline

3.2.1 The strategies of searching

1) Keyword: Narrowband UVB, seborrheic dermatitis, ultraviolet, Phototherapy, broadband UVB, Psoralen plus Ultraviolet A (PUVA), light

2) Medical Subject Headings: Mesh term

3) Snowballing technique to increase the number of the related studies.

4) other sources such as review articles, google scholar

3.2.2 Study appraisal

To appraise the studies, we will use the GRADE approach to value the study individually. Also, the PRISMA checklist 2020 (Table 3.1) is being used in order to clarify the details of the studies as well as Cochrane Public Health Group Data Extraction and Assessment.

3.2.3 Risk of Bias

We will grade the risks of bias to 3 level – Good quality, Fair quality and poor quality. In term of cohort study/case control study, The New Castle-Ottawa scale form Cochrane Collaboration (table2.) will be used to adjust the data.

3.3 Types of participants

Inclusion criteria -All the study which is about having used phototherapy to treat seborrheic dermatitis

Exclusion - the study is not about the phototherapy treatment in seborrheic dermatitis

3.4 Outcome

3.4.1 Primary outcome

1) Remission rate
2) Recurrent rate

3.4.2 Secondary outcome

1) Side effects of phototherapy therapy

3.5 Data analysis

Relative risk (RR), 95% confidence Interval(95%CI) are being used with the dichotomous outcome. Mean Difference (MD) or Standard Deviation (SD) are being used with the continuous data. So, after having the result, we will adjust the value by using p-value lesser than 0.1. In the other hand, the data which is unable to analysis, the quality of the data will be analyzed to be subgroup (Meta-analysis/ Subgroup analysis).

We use the flow chart from PRISMA 2020 to draw the diagram and the conclusion of the studies.

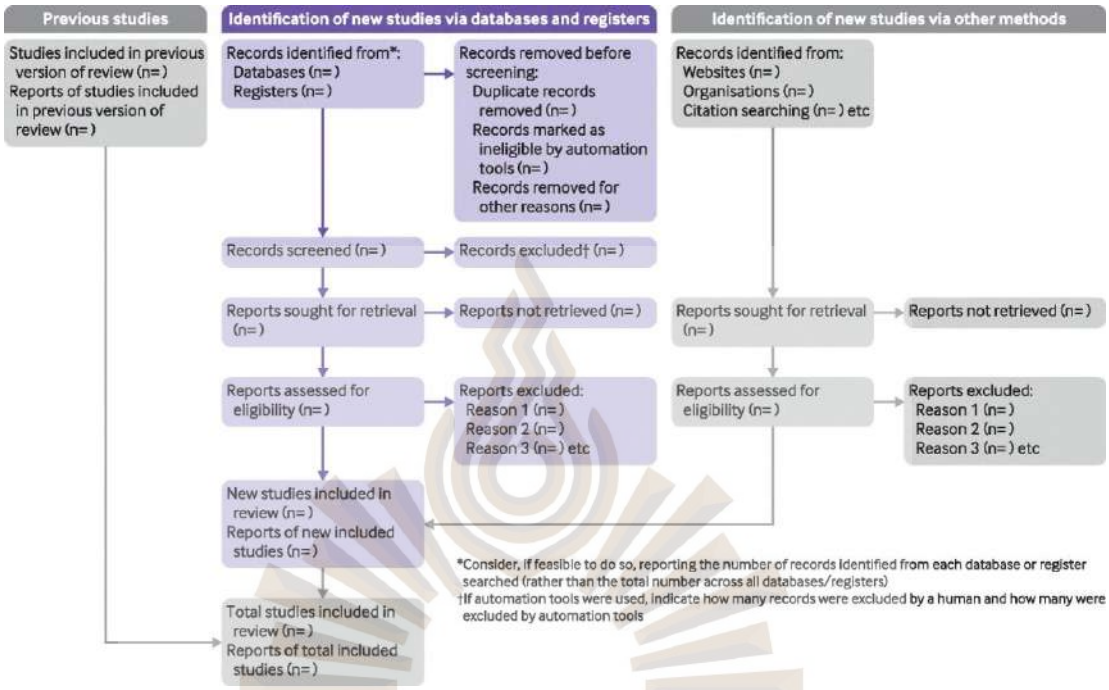

Figure 3.1 PRISMA 2020 flow diagram template for systematic reviews.

Table 3.1 The Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.

Table 3.1 The Cochrane Collaboration's tool for assessing risk of bias (Cont.)

Domain	Support for judgement	Review authors' judgement
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.

Table 3.1 The Cochrane Collaboration's tool for assessing risk of bias (Cont.)

Domain	Support for judgement	Review authors' judgement
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Chapter 4

Research results

4.1 Study Characteristics

Following the extensive search process, 65 records were initially retrieved. Subsequent stages involved the removal of duplicate records, meticulous screening, and a thorough assessment of full-text articles, in which we found 35 records from the PubMed, 27 records from Medline and three records from the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library based on the keywords.Subsequent stages involved the removal of duplicate records, meticulous screening, and a thorough assessment of full-text articles. It's worth noting that a significant portion of the search results, obtained through keyword queries in databases, did not directly pertain to seborrheic dermatitis; rather, they were associated with atopic dermatitis and psoriatic dermatitis. Furthermore, among the screened studies, two were represented solely by abstracts without accessible full texts(), and one had an abstract in English with the full text available only in Korean. The PRISMA flow was demonstrated in Figure 4.1.

In total, three studies were included in this systematic review, encompassing two prospective single-arm trials and one randomized trial featuring three arms. The focus of these studies was exclusively on adults, with a median age of 32 years, spanning from 6 months to 61 years old. The interventions across these studies exhibited a median duration of 12 weeks, with exposure periods ranging from 6 to 47 weeks. Additional details regarding the characteristics of the included studies are comprehensively outlined in Table 4.1. It is noteworthy that each study employed distinct forms of light therapy, introducing variations such as intense pulse therapy, narrowed band UVB, and green diode light therapy. However, the lack of homogeneity among these interventions and study designs precludes the feasibility of conducting a further meta-analysis. As

such, a narrative synthesis will be employed to effectively present the diverse findings and outcomes within the constraints of this systematic review.

4.2 Quality of included studies

The included studies posed a low to moderate risk of bias. The common risk was that no study could blind interventions and only one study has comparison groups. Figure 4.1 shows other issues of methodological quality in the included studies.

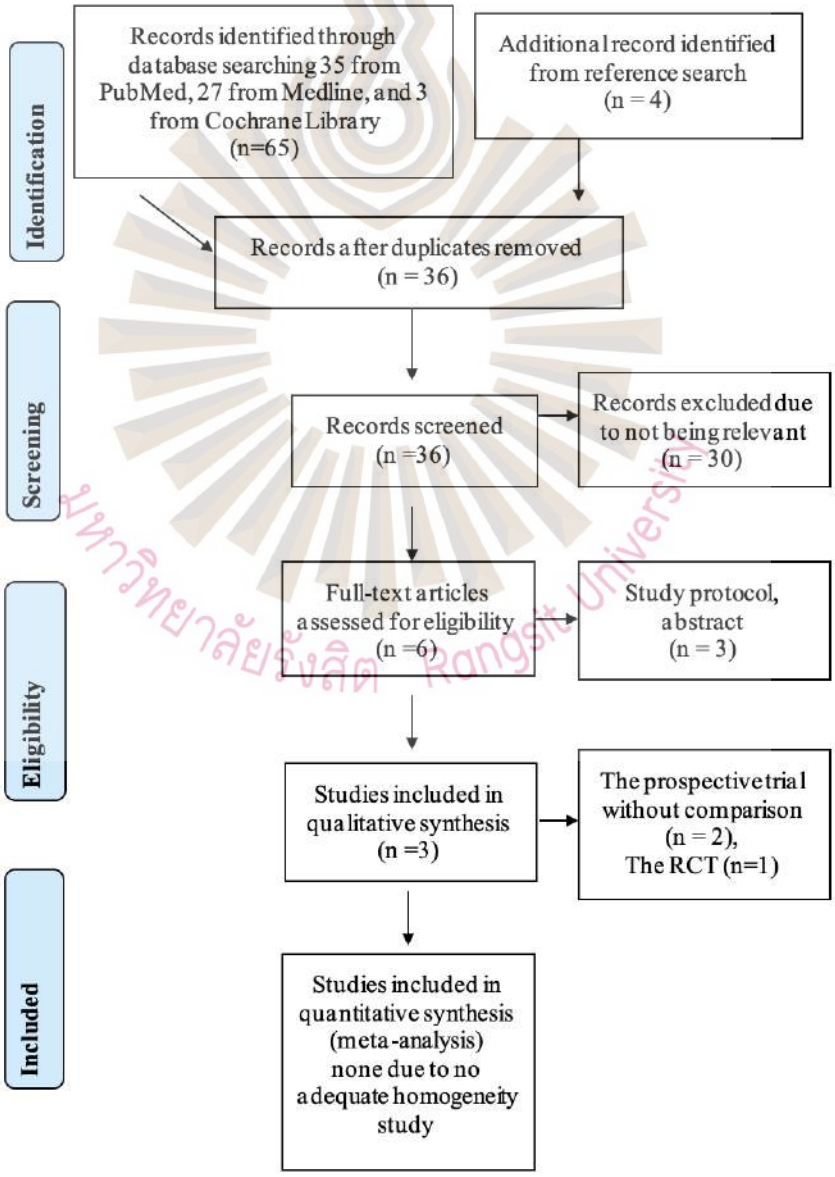

Figure 4.1 Algorithm of study selection following PRISMA guideline

Table 4.1 The characteristic of included studies

Paper	Population characteristics	Intervention	Outcome measured	Study design and duration	Main findings
Clinical study on treatment of facial seborrheic dermatitis with intense pulsed light combined with 30% supramolecular salicylic acid (Gu and Wang.,2020)	Patients with mild or moderate facial seborrheic dermatitis, with a higher proportion of female patients, aged 20-41 years, and specific exclusion criteria related to allergies, recent medication use, and other health conditions. Total: 45 (15:15:15)	Combination of IPL and 30% supramolecular salicylic acid treatment compared with IPL treatment alone and 30% supramolecular salicylic acid treatment alone	Improvement in symptoms of seborrheic dermatitis after the treatments	Randomized nonblinded trial The duration of the intervention in this study is approximately 46-47 weeks (11-12 months), based on the treatment occurring once every 4 weeks in three consecutive rounds and the average treatment course of 15.3-15.4 months.	- The combination of IPL and 30% supramolecular salicylic acid showed significant improvement in symptoms of seborrheic dermatitis 4 weeks after the first treatment, with a quicker and more effective result compared to individual treatments. - After three rounds of treatments, the combination group had significantly higher efficacy in decreasing seborrheic dermatitis compared to the IPL group and the 30% supramolecular salicylic acid group. - The combination of IPL and 30% supramolecular salicylic acid was effective in treating facial seborrheic dermatitis and provided a quicker result with no adverse reactions.

Table 4.1 The characteristic of included studies (Cont.)

Paper	Population characteristics	Intervention	Outcome measured	Study design and duration	Main findings
Narrow-band ultraviolet B (TL-01) phototherapy is an effective and safe treatment option for patients with severe seborrhoeic dermatitis. (Pirkhammer et al., 2000)	Patients with severe seborrhoeic dermatitis, age range from 6 months to 24 years, treatment performed during different seasons, some patients underwent HIV testing and had negative results Total: 18	narrow-band ultraviolet (UV) B (TL-01) phototherapy, administered three times weekly for up to a maximum of 8 weeks. The dose of the intervention started at 70% of the minimal erythema dose (MED) and was adjusted based on	Clinical score assessing erythema, scaling, infiltration, and pruritus at baseline and every 2 weeks, median clinical score decrease from baseline to after 8 weeks of treatment, intensity of pruritus measured on a visual	Prospective nonblinded trial The duration of the intervention in the study was 7.4 weeks (range 2.6-8 weeks).	Narrow-band UVB phototherapy is highly effective and safe for treating severe seborrhoeic dermatitis, with all patients showing favorable responses, including complete clearance and marked improvement. The median clinical score and pruritus score significantly decreased after 8 weeks of treatment, indicating the effectiveness of narrow-band UVB phototherapy in reducing the symptoms of seborrhoeic dermatitis. Despite the positive response to treatment, relapses occurred in all patients after a median of 21 days, suggesting the need for a maintenance schedule to prolong remission.

Table 4.1 The characteristic of included studies (Cont.)

Paper	Population characteristics	Intervention	Outcome measured	Study design and duration	Main findings
		the erythemal reaction to the previous exposure. The median cumulative narrow-band UVB dose applied to the patients was 9´8 J cm 22 (range 2´9± 22´2), and the median number of exposures was 23 (range 9±24) with a median duration of treatment of 7´4 weeks (range 2´6±8).	analogue scale, median pruritus score decrease from baseline to week 8, time to relapse after treatment		

Table 4.1 The characteristic of included studies (Cont.)

Paper	Population characteristics	Intervention	Outcome measured	Study design and duration	Main findings
A new therapeutic option for facial seborrhoeic dermatitis: indole-3-acetic acid photodynamic therapy (Kwon, Youn, and Park.,2012)	Population characteristics: - Age range: 26 to 51 years - Gender: all female - Fitzpatrick skin type: III or IV Total: 23	The intervention(s) that the study participants received are: - 0.015% IAA (AC gel Ò; Wellskin, Seoul, Korea) applied for 15 minutes under occlusion - 520-nm green diode light (Nouvo-GB Ò; M.I tech, Daejeon, Korea)	Seborrhoeic dermatitis Area and Severity Index (SASI), patient's assessment of the symptoms (itchiness, burning, erythema, scale, and tightness), sebum secretion rate, Erythema Index (EI), and physician's	Prospective, single-blinded, trial The duration of the intervention in the study was 6 weeks, consisting of three treatment sessions with 1-week intervals, and the therapeutic effects were observed to be maintained for 4 weeks after	IAA-PDT is a safe and effective therapeutic option for facial seborrheic dermatitis.

Table 4.1 The characteristic of included studies (Cont.)

Paper	Population characteristics	Intervention	Outcome measured	Study design and duration	Main findings
		with an intensity of 9 J/cm 2 illuminated for 15 minutes - The treatment protocol was repeated three times with 1-week intervals.	photographic assessment	the last treatment session.	

Table 4.2 Results of the risk of bias assessment

Domain	Gu and Wang (2020)	Pikhammer et al. (2000)	Kwon, Youn, and Park (2012)
Random sequence generation.	+	-	-
Allocation concealment.	0	-	-
Blinding of participants and personnel	-	-.	-
Blinding of outcome assessment	-	-	-
Incomplete outcome data -	+	0	0
Selective reporting.	0.	0	0
Other sources of bias.	+	0	0
Summary quality	medium	poor	poor

+ = yes or low risk of bias

0 = unclear or unknown risk of bias

- = no or high risk of bias

Figured 3: the results of the risk of bias assessment.

In our analysis of the research by Gu and Wang (2020), it was observed that the study demonstrated a low risk of bias in random sequence generation and other bias sources. However, there was not enough information to determine if the allocation to treatment groups was hidden, which creates some uncertainty. Both the participants and those administering treatments likely knew which treatment was being given, raising concerns about potential biases in how the outcomes were perceived and reported. Similarly, the people assessing the results were probably aware of who received which treatment, which could skew their evaluations. On a positive note, the study did a good

job of reporting all of the outcomes they set out to measure, and there were no additional biases found, suggesting a generally reliable approach in these areas. Overall, considering these strengths and weaknesses, the study's quality is deemed medium. The study by Pirkhammer et al. (2000) reveals certain limitations in its risk reporting, with many domains showing unclear or high risks, raising concerns about the study's reliability. The lack of explicit mention of random sequence generation or allocation concealment raises questions about the study's effectiveness in preventing selection bias. Furthermore, the absence of detailed blinding procedures suggests potential risks of performance and detection bias. The study indicates that every participant showed improvement following the treatment, and it tracked their progress until any recurrence or notable worsening of the condition. However, there were six patients who did not complete the study but were still counted in the final analysis using an intention-to-treat approach. This method helps reduce the impact of missing data but does not completely eliminate concerns, especially if these patients stopped participating due to issues related to the treatment itself. This situation raises some questions about the completeness and reliability of the study's outcome data. The lack of explicit information on whether all pre-specified outcomes were reported introduces uncertainty regarding selective reporting. Additionally, the absence of detailed descriptions of other study design elements makes it challenging to fully evaluate the potential for other biases. In summary, while Pirkhammer et al.'s study provides valuable insights into the efficacy of narrowband UVB phototherapy for seborrheic dermatitis, the absence of comprehensive methodological details necessitates a cautious interpretation of the findings. A more thorough methodological disclosure is essential to fully assess the risks of various biases and validate the study's conclusions (Pirkhammer et al., 2020). The investigation conducted by Kwon, Youn, and Park (2012) lacks explicit methodological disclosures regarding random sequence generation and allocation concealment. This omission introduces ambiguity concerning the unbiased nature of treatment allocation, raising potential concerns about the influence of selection bias on the study's outcomes. Furthermore, the absence of detailed reporting on blinding protocols for participants and personnel is noteworthy, given its critical role in mitigating performance bias—a form of bias that arises when the knowledge of treatment allocation influences behaviors or outcome assessments. The clarity is similarly deficient regarding the blinding of

outcome assessors, an essential aspect to prevent detection bias, where foreknowledge of treatment assignments could affect outcome evaluations. The study does not thoroughly articulate how it managed instances of incomplete outcome data, an issue pivotal for ensuring the integrity of the research findings. Incomplete data, if not properly addressed, can distort the study's conclusions, particularly concerning the efficacy of the treatment under investigation. Concerning selective reporting, the study falls short of confirming whether all predetermined outcomes and analyses were comprehensively reported. The absence of such confirmation may lead to suspicions of selective reporting bias, where only selected outcomes—potentially those that are favorable— are disclosed, while others are neglected. Lastly, the paper does not delve into potential additional biases, leaving readers to speculate about other unaddressed factors that might skew the results. The failure to acknowledge or control these potential biases further complicates the interpretation of the study's validity. In conclusion, the paucity of methodological transparency and the unaddressed risk of various biases in the study by Kwon, Youn, and Park (2012) suggest a poor level of quality. While the research provides insights into the treatment of facial seborrheic dermatitis, the identified methodological shortcomings necessitate a prudent approach to interpreting its findings, underscoring the imperative for rigorous methodological rigor in clinical research. To summarize, the quality assessment (Table 4.2) of the included studies revealed varied bias risk levels. Gu and Wang (2020) was assessed as having medium quality, with some low and unclear bias risks. In contrast, Pirkhammer et al. (2000) and Kwon, Youn, and Park (2012) were rated as poor, displaying unclear and high bias risks across several domains.

4.3 Synthesis of the results

Phototherapy techniques, including narrow-band ultraviolet B (TL-01) phototherapy, intense pulsed light (IPL) combined with 30% supramolecular salicylic acid, and photodynamic laser, have shown effectiveness in managing seborrheic dermatitis, supported by studies conducted by Pirkhammer et al., (2000), Gu and Wang (2020), and Kwon, Youn, and Park (2012). These interventions have demonstrated significant alleviation of symptoms and a reduction in the severity of the condition.

However, it is crucial to recognize that the underlying pathological mechanisms of seborrheic dermatitis primarily involve Malassezia proliferation and inflammation. The prevailing conventional treatment involves the application of topical antifungal and anti-inflammatory agents, as emphasized by Borda.

While the initial evidence suggests the effectiveness of phototherapy treatments, it is important to consider them as integral components within a comprehensive treatment strategy that may include these alternative agents. Nevertheless, the existing evidence is notably limited in both quantity and quality. Therefore, a large-scale randomized controlled trial is warranted to establish the efficacy of phototherapy in treating seborrheic dermatitis.

4.4 Discussion

The use of phototherapy in the management of seborrheic dermatitis (SD) has been a subject of discussion and investigation. Here, we delivery into the key points in the discussion about phototherapy as a treatment modality for SD.

There are few studies have reported positive outcomes with phototherapy in the treatment of seborrheic dermatitis. Patients have shown improvement when exposed to natural sunlight during the summer months, and specific phototherapy methods, such as narrow-band UVB, have demonstrated efficacy. The previous across various skin conditions, including psoriasis, atopic dermatitis, mycosis fungoides, and vitiligo, have suggested that narrow-band UVB is more effective than broadband UVB. This comparative effectiveness supports the consideration of narrow-band UVB in the treatment of seborrheic dermatitis.

The hypothetic mechanism of narrow-band UVB, is believed to induce cellular and molecular changes in the skin. It leads to photochemical reactions that transform chromophores into photoproducts, resulting in cell cycle arrest and apoptosis. Reduced cell proliferation, immunosuppression, and T cell apoptosis are thought to contribute to the suppression of disease activity in inflammatory skin conditions like seborrheic

dermatitis. Phototherapy can be considered as part of a comprehensive treatment plan for seborrheic dermatitis. Combining phototherapy with topical treatments or other therapeutic modalities may enhance overall efficacy. Meanwhile there were some evidence claimed that PUVA and natural sunlight may worsen seborrheic dermatitis.

The Phototherapy, when administered correctly, has generally demonstrated a favourable safety profile. Studies, such as the one by Pirkhammer et al. (2020), have found narrow-band UVB to be both effective and safe for patients with severe seborrheic dermatitis. While adverse effects are generally minimal, occasional moderate erythema post-exposure has been reported in some cases. It is crucial to carefully monitor patients for any adverse reactions and adjust the treatment plan accordingly. The success of phototherapy is contingent on patient compliance. Factors such as the frequency and duration of sessions should be tailored to individual patient needs and preferences Need for Further Research: Despite positive findings, there is a need for additional well-designed studies to further establish the efficacy, safety, and optimal protocols of phototherapy in seborrheic dermatitis. Research should explore long-term outcomes, patient subgroups, and potential synergies with other treatment modalities.

In conclusion, while phototherapy, particularly narrow-band UVB, has shown promise in the treatment of seborrheic dermatitis, ongoing research is essential to strengthen the evidence base, refine treatment protocols, and address individual patient variations in response. A multidisciplinary approach, involving dermatologists, researchers, and patients, is crucial for advancing our understanding and optimizing the use of phototherapy in the management of seborrheic dermatitis. It has been demonstrated that patients experience improvement when exposed to natural sunlight during the summer months. Additionally, two studies have indicated the positive effects of treatment involving selective ultraviolet (UV) phototherapy or oral photochemotherapy. Nevertheless, it is noteworthy that psoralen and ultraviolet A therapy may trigger seborrheic dermatitis (SD).

Chapter 5

Conclusion and recommendations

5.1 Summary

The systematic review aims to explore the effectiveness of phototherapy in treatment of seborrheic dermatitis from, 39 records were initially identified and the three studies were ultimately included, consisting of two prospective single-arm trials and one randomized trial with three arms. The study participants were exclusively adults, with a median age of 32 years, ranging from 6 months to 61 years old. The interventions in these studies had a median duration of 12 weeks, with exposure periods spanning from 6 to 47 weeks. In summary there are three phototherapy that has evident support its efficacy including

1) Narrow-Band Ultraviolet B (TL-01) Phototherapy:

TL-01 phototherapy involves the use of a specific wavelength of ultraviolet B (UVB) light. Studies have suggested that TL-01 phototherapy can lead to significant improvement in symptoms and a reduction in the severity of seborrheic dermatitis.

2) Intense Pulsed Light (IPL) Combined with 30% Supramolecular Salicylic Acid: IPL uses a broad spectrum of light to target various skin concerns, and when combined with supramolecular salicylic acid, it aims to address seborrheic dermatitis.This combination has demonstrated efficacy in improving symptoms associated with the condition.

3) Photodynamic Laser Therapy: Photodynamic therapy involves the use of a photosensitizing agent, which is activated by laser light to target affected skin areas.

In addition, certain lasers, such as Picosecond Nd:YAG laser, have been investigated for their effectiveness in managing seborrheic dermatitis.

However, due to the lack of homogeneity among these interventions and study designs, conducting a meta-analysis is not feasible. Therefore, a narrative synthesis will be employed to effectively present the diverse findings within the confines of this systematic review. Regarding the quality of the included studies, they exhibited a low to moderate risk of bias. A common risk factor was the inability of studies to blind interventions, and only one study included comparison groups.

5.2 Suggestion for the clinical use

Based on our systematic review, the phototherapy can be considered as a treatment option for seborrheic dermatitis, particularly in cases where standard treatments have shown limited efficacy or when patients prefer non-topical or non-pharmacological approaches. Here are some suggestions for the clinical use of phototherapy in seborrheic dermatitis:

The severity: Phototherapy may be more suitable for mild to moderate cases of seborrheic dermatitis. Severe cases may still require traditional treatments, and phototherapy can be considered as an adjunct.

Type of Phototherapy: the most reliable evidence is Narrowband UVB (NB-UVB): It may be a preferred choice due to its effectiveness and reduced risk of side effects compared to broader UVB spectra. Combining with Topical Treatments, such as antifungal agents or anti-inflammatory creams, to enhance overall therapeutic outcomes.

Monitoring and Follow-up: Conduct regular assessments to monitor the patient's response to phototherapy. Adjust the treatment plan as needed based on the individual's progress. The ongoing education to patients about the benefits, risks, and expectations associated with phototherapy. Emphasize the importance of adherence to the treatment schedule.

Adverse Effects from phototherapy in seborrheic dermatitis is rare and mild. The eye and skin protection would mitigate the complication as well as the regular monitor patients for any adverse effects, such as erythema or photosensitivity reactions. Adjust the treatment plan if side effects occur.

It's essential to approach the clinical use of phototherapy in seborrheic dermatitis with a comprehensive understanding of the patient's medical history, preferences, and the specific characteristics of their skin condition. Always tailor the treatment plan based on individual needs and regularly reassess the patient's response to therapy. Additionally, staying informed about the latest research and guidelines in phototherapy for dermatological conditions is crucial for providing the best possible care.

5.3 Suggestion for further research

Our systematic review suggest potential areas of knowledge gaps regarding phototherapy in seborrheic dermatitis as following;

Optimal Treatment Protocols: While phototherapy has shown promise in managing seborrheic dermatitis, there may be a lack of standardized treatment protocols. Further research is needed to determine the most effective parameters for light therapy, including the ideal wavelength, duration of sessions, and frequency of treatments.

Long-Term Efficacy and Safety: The long-term efficacy and safety of phototherapy for seborrheic dermatitis need more exploration. Understanding the durability of treatment effects and potential side effects over extended periods can provide valuable insights.

Comparative Studies: Comparative studies that directly compare phototherapy with other standard treatments for seborrheic dermatitis, such as topical antifungals or corticosteroids, can help establish its relative effectiveness and inform treatment guidelines.

Patient Subgroups: Research may explore whether certain subgroups of patients with seborrheic dermatitis, such as those with specific demographics, comorbidities, or disease severities, respond differently to phototherapy. This could help tailor treatment approaches based on individual characteristics.

Mechanisms of Action: While the broad understanding is that phototherapy modulates immune responses and has anti-inflammatory effects, more detailed investigations into the precise mechanisms of action at the cellular and molecular levels could deepen our understanding.

Combination Therapies: Exploring the potential synergies or additive effects of combining phototherapy with other treatment modalities, such as topical agents or systemic medications, could be valuable in optimizing therapeutic outcomes.

Home-Based Phototherapy: Investigating the feasibility and efficacy of home-based phototherapy devices for seborrheic dermatitis could expand treatment options and improve patient accessibility. However, this would need careful consideration of safety and adherence.

Patient-reported Outcomes: Comprehensive studies assessing patient-reported outcomes, including quality of life, satisfaction, and adherence, can provide a more holistic understanding of the impact of phototherapy on individuals with seborrheic dermatitis.

Pediatric Population: Research on the use of phototherapy in pediatric populations with seborrheic dermatitis is limited. Studies addressing safety, efficacy, and tolerability in children would be beneficial.

Cost-effectiveness: Evaluating the cost-effectiveness of phototherapy compared to other treatment options for seborrheic dermatitis can influence healthcare decisions and resource allocation.

5.4 Conclusions

Phototherapy has emerged as a promising modality for managing various dermatological conditions, including seborrheic dermatitis. Among the different phototherapy techniques, narrow-band ultraviolet B (TL-01) phototherapy, intense pulsed light (IPL) combined with 30% supramolecular salicylic acid, and photodynamic therapy (PDT) with laser, have shown initial evidence of efficacy in treating seborrheic dermatitis.

Narrow-band UVB (NB-UVB) phototherapy, utilizing the TL-01 lamp, has been demonstrated to reduce inflammation and normalize the abnormal proliferation of keratinocytes, which are hallmark features of seborrheic dermatitis. The specific wavelength of NB-UVB (311-313 nm) allows for targeted therapeutic effects while minimizing the risk of adverse outcomes associated with broad-spectrum UVB phototherapy.

Intense pulsed light (IPL) combined with 30% supramolecular salicylic acid represents another innovative approach. IPL emits a range of wavelengths (500-1200 nm) that can penetrate the skin and target chromophores such as melanin and hemoglobin. The addition of supramolecular salicylic acid enhances the phototherapeutic effect by improving the penetration and efficacy of the light energy, leading to a reduction in sebaceous gland activity and inflammation.

Photodynamic therapy (PDT) with laser involves the application of a photosensitizing agent, followed by exposure to a specific wavelength of light. This process generates reactive oxygen species that selectively target and destroy abnormal cells. PDT has shown promise in managing seborrheic dermatitis by reducing erythema,

scaling, and pruritus, potentially through its anti-inflammatory and immunomodulatory effects.

Despite these promising initial findings, the current body of evidence supporting the use of phototherapy in seborrheic dermatitis is limited in both quantity and quality. Most studies to date have been small-scale, open-label, or observational, lacking the rigorous design required to draw definitive conclusions about efficacy and safety. Therefore, there is a compelling need for large-scale, randomized controlled trials (RCTs) to establish the clinical efficacy, optimal treatment parameters, and long-term safety of these phototherapeutic interventions.

RCTs should be meticulously designed to include diverse patient populations, standardized treatment protocols, and robust outcome measures. Endpoints should encompass both clinical and patient-reported outcomes, such as the severity of erythema, scaling, pruritus, and overall quality of life. Additionally, mechanistic studies exploring the underlying biological effects of phototherapy on seborrheic dermatitis could provide valuable insights into optimizing treatment strategies.

In conclusion, while preliminary evidence suggests that narrow-band UVB phototherapy, IPL combined with supramolecular salicylic acid, and PDT with laser may be effective in managing seborrheic dermatitis, the need for high-quality, large-scale RCTs is paramount. Such studies are essential to validate these findings, inform clinical practice, and ultimately improve patient outcomes in the management of seborrheic dermatitis.

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