PHOTOTOXIC REACTION COMPLICATED FROM PHOTOTHERAPY IN THAI PATIENTS WITH DERMATOLOGICAL DISEASES: A RETROSPECTIVE STUDY

BY

KIATTISAK SANTIPAS

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Abstract

The phototoxic reaction is one of phototherapy's most significant adverse effects. This retrospective, single-center study in the dermatology department aims to describe the prevalence of phototoxic reactions related to phototherapy in Thai patients.

All phototherapy patients in this study had 64,629 collective sessions between October 2015 and September 2020. The 200 sessions (0.3%) with phototoxic responses were associated with phototherapy. The dermatosis with the most significant incidence of phototoxic reactions was vitiligo (54%). The most common cause of phototoxicity stemmed from patient variables, including compliance issues such as excessive exposure to sunlight (9%), medication (8.5%), loss of treatment (6%), underwear displacement from the previous visit (2.5%), rubbing the lesion (2.5%), wearing various protective sizes (2.5%), failure to apply sunscreen (2%) concurrent disease (2%), and unknown cause (16.5%). The subsequent treatment protocol was the most significant cause, accounting for 49.5%. Technical error constituted the final 2.5%. The dermatologist needs to recognize when to continue increasing the dose and to emphasize to the patient they must comply with the treatment.

(Total 56 pages)

Keywords: Phototoxic reaction, Adverse events, Phototherapy, Narrowband UVB, Excimer lamp, Psoralen plus UVA

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Chapter 1

Introduction

1.1 Background and Significance of the Problem

Light-based treatments have transformed therapeutic strategies in dermatology over the past hundred years. From ancient times, the effects of UV radiation on the human skin were employed to treat various skin conditions. The esteemed Galen advised those with skin ailments to bask longer under the sun. During the colonial era, British doctors noted a marked improvement in the condition of psoriasis patients who spent time in India. Yet, it took several more decades for structured light therapies to emerge. In 1903, Niels Ryberg Finsen, a dermatologist from the Faroe Islands, was awarded the Nobel Prize in Medicine for his pioneering work using concentrated light radiation to treat diseases, notably lupus vulgaris, marking a significant advancement in medical science. The advent of modern UV lamps sparked the evolution from natural sun treatments to today's advanced phototherapies.

Phototherapy harnesses the power of ultraviolet (UV) light to treat various skin disorders such as psoriasis, vitiligo, atopic dermatitis, and more. Modern phototherapy involves a range of UV radiation techniques, from broadband UVB (290-230 nm) and narrowband UVB (311-313 nm) to the 308 nm excimer laser and UVA1 (340-400 nm). Additionally, treatments may employ UVA (320-400 nm) combined with psoralens (PUVA) or even use UVA on its own (Honigsmann & Schwarz, 2018; Singer & Berneburg, 2018).

Phototherapy, while effective, can also result in adverse reactions, both phototoxic and photoallergic. Phototoxic reactions arise when certain topically or systemically applied medications or metabolites interact with light, causing direct

cellular damage. This can happen to anyone, provided they're exposed to the right amounts of the agent and the activating light wavelengths. Photoallergic reactions, on the other hand, manifest as delayed hypersensitivity responses to a photon-modified molecule. Common manifestations of phototoxic reactions range from an intense sunburn sensation to other symptoms like blisters, uneven skin pigmentation, skin cancer, and hastened photoaging. Factors influencing these reactions include UV exposure intensity, lack of protective measures, skin type, and certain medications (Pereira, Xará, & Gonçalo, 2022; Henry, 2019; Ibbotson, 2018).

In psoriasis treatment, research supports PUVA's superior effectiveness over NB-UVB for plaque-type psoriasis (Singer & Berneburg, 2018; Elmets et al., 2020; Gordon, Diffey, Matthews, & Farr, 1999). Although PUVA has shown better results, its association with skin cancer after prolonged use has made it less favored. NBUVB, conversely, has shown no harmful effects on pregnant women or Asian children. For milder cases, the 308-nm Excimer laser is recommended for limited skin areas (Kemény, Varga, & Novak, 2019; Matos, Ling, & Sheth, 2016).

Numerous studies advocate for NB-UVB over other phototherapy types for vitiligo due to its effectiveness and safety profile compared to PUVA. Evidence also suggests excimer laser's edge over NB-UVB in treating vitiligo (Esmat et al., 2017; Thu et al., 2019; Bae et al., 2017).

Atopic dermatitis (AD) patients resort to phototherapy mainly when first-line treatments don't yield results (Rodenbeck, Silverberg, & Silverberg, 2016). While some studies show NB-UVB outperforming UVA-1, others indicate little difference. The 308 nm Excimer laser is also beneficial for stubborn AD patches. Importantly, NBUVB's safe usage in pediatric patients is well-documented (Ortiz-Salvador, & Pérez-Ferriols, 2017).

Despite its controlled and conventional use, phototherapy's adverse effects are noteworthy. The Institute of Dermatology in Thailand reported a rising trend in phototoxicity cases, an increase of an average of 40 new cases per year. To maximize

the therapy's benefits, it's crucial to understand and prevent these phototoxic reactions, especially in sun-intensive regions like Thailand. A deeper dive into phototoxic reactions' prevalence and risk factors is necessary, as such insights are currently lacking. This study at the Institute of Dermatology, Thailand, attempts to bridge that gap.

1.1.1 Interactions of UV Radiation with Tissue

The Earth's atmosphere acts as a protective shield, selectively filtering out specific wavelengths of solar radiation. While the ozone layer virtually eliminates the UVC spectrum, ensuring its absence from our discussion, a significant portion of UVB rays are similarly intercepted by atmospheric components, allowing only a limited amount to reach our skin. The influence of phototherapy on human skin varies based on the specific UV wavelength in use. Though UVA rays are less energetic, they delve deeper into the skin, affecting even the inner layers of the dermis. In contrast, UVB radiation primarily targets the outer skin layer, the epidermis, and the topmost part of the dermis.

1.1.2 Phototherapy with UVB

UVB phototherapy employs artificial UVB light without external photosensitizing agents. The radiation is absorbed by endogenous chromophores in the skin, leading to photochemical reactions. These reactions with UV-absorbing biomolecules result in various biological effects, culminating in therapeutic outcomes. A primary chromophore for UVB is nuclear DNA. When UV rays are absorbed by nucleotides, DNA photoproducts, chiefly pyrimidine dimers, form.

One therapeutic use of UVB exposure is to curb excessive DNA synthesis, like in the rapidly increasing epidermal cells in psoriasis. Moreover, UVB triggers the tumor suppressor gene TP53. This activation can cause cells to pause their growth cycle, giving room for DNA repair, or initiate apoptosis in keratinocytes—often called

"sunburn cells"—if DNA damage is irreparable. By these mechanisms, p53 acts as a safeguard against the development of skin cancers.

Beyond affecting cellular processes, UVB exposure releases several signaling molecules, such as prostaglandins and cytokines. Notably, Interleukin-6 (IL-6) and Interleukin-1 (IL-1) play roles in UV phototoxicity symptoms like sunburn and immune suppression, respectively. Interestingly, these effects might also be pivotal for the therapy's success (Honigsmann & Schwarz, 2018).

Two primary UVB modalities exist. One utilizes the complete UVB spectrum between 280-320 nm (broadband UVB therapy). In comparison, the other focuses on a specific wavelength of 311 nm (narrowband UVB therapy or UVB 311). The narrowband approach was developed to enhance UVB treatment's safety by sidestepping the potentially harmful lower wavelengths with more energy. Given its efficacy and safety, UVB311 stands out in managing conditions like psoriasis, atopic dermatitis, and vitiligo, and preventing reactions like polymorphic light eruption (Singer & Berneburg, 2018).

Over decades, UVB phototherapy has cemented its place in psoriasis treatment and continues to evolve. Even though narrowband UVB remains the preferred phototherapy for psoriasis, in severe cases, PUVA therapy might show better results (Singer & Berneburg, 2018).

1.1.3 Phototherapy with UVA1

The UVA spectrum, spanning 320–400 nm, is split into two categories: UVA1 (340–400 nm) and UVA2 (320–340 nm). This distinction was primarily based on the observation that UVA2 mimics UVB in producing skin redness (erythema), modulating immune responses, and initiating photocarcinogenic processes. Due to its extended wavelength, UVA1 penetrates deeper into the skin than UVA2, impacting not just the epidermal layer but also reaching the middle and deep sections of the dermis, notably affecting blood vessels.

Considering the vast expanse of the skin as an organ, UVA1 exposure can significantly influence circulating immune cells, leading to systemic effects. Its capacity to induce apoptosis in T-lymphocytes is particularly notable and potentially beneficial in managing conditions like atopic dermatitis and possibly Mycosis Fungoides. UVA1 exposure can also diminish the count of Langerhans cells and mast cells in the dermis, relevant for conditions like atopic dermatitis and cutaneous mastocytosis. Furthermore, studies have highlighted increased collagenase expression in treated sites of localized scleroderma after UVA1 exposure. This might partly explain the effectiveness of UVA1 in addressing localized scleroderma and related sclerotic conditions (Honigsmann & Schwarz, 2018).

The primary applications of UVA1 phototherapy encompass conditions like atopic dermatitis and sclerotic skin diseases. When addressing atopic dermatitis, high-dose UVA1 and narrowband UVB therapies are comparable in effectiveness and patient tolerance. However, oral PUVA therapy is superior to both in terms of effectiveness (Singer & Berneburg, 2018).

1.1.4 Phototherapy with Psoralens (PUVA)

Psoralen photochemotherapy, or PUVA, represents a therapeutic combination of psoralens (P) and long-wave ultraviolet radiation (UVA). The combined effect of these two entities yields a therapeutically advantageous phototoxic response, an outcome not achievable when either component is used independently. The administration of psoralens can either be oral or topical, the latter through solutions, creams, or bath preparations, followed by exposure to UVA.

Originating as linear furocoumarins, psoralens naturally manifest in a plethora of plants. Beyond their natural presence, several synthetic formulations of psoralens also exist. 8-MOP (methoxsalen) is predominantly employed for oral and topical (bath and cream) PUVA procedures. Notably, while 8-MOP has botanical roots, it is also synthesized artificially. An alternative synthetic compound, 4,5′,8-trimethylpsoralen (TMP or trioxsalen), exhibits a peculiar behavior: its phototoxicity

is subdued compared to 8-MOP when administered orally but intensifies when used in bath preparations. TMP's primary utilization for bath PUVA is observed in Scandinavia. Another variant, 5-Methoxypsoralen (5-MOP or bergapten), when taken orally, is less likely to cause erythema and doesn't trigger gastrointestinal issues. Yet, in specific European locales, its extensive use has been linked to high liver metabolization rates during the drug's initial pass, potentially negating its therapeutic potential (Honigsmann, & Schwarz, 2018).

Mechanistically, PUVA therapy halts the cell cycle and promotes apoptosis, with lymphocytes being the primary target (Singer, & Berneburg, 2018). PUVA has a commendable track record, particularly in treating psoriasis patients. In cases of severe psoriasis, PUVA's efficacy is unparalleled compared to other phototherapy modalities, catering to plaque and pustular variations. Additionally, atopic dermatitis patients also benefit remarkably from PUVA. However, this efficacy comes with a caveat. Of all phototherapeutic forms, PUVA is notorious for inflicting maximal DNA damage and elevating carcinogenic risks. Hence, when weighing risks against benefits, the primary therapeutic alignment for PUVA is towards conditions like mycosis fungoides and lymphomatoid papulosis.

1.2 Research Objectives

To describe the prevalence, characteristics and cause of phototoxic reactions in Thai patients who receiving phototherapy at Phototherapy center, Institute of Dermatology, Bangkok, Thailand (A five-year study, 2015 - 2020).

1.3 Research Questions/ Assumptions

Can the summer season influence phototoxic reactions in places with extensive sun exposure, such as Thailand?

1.4 Research Framework

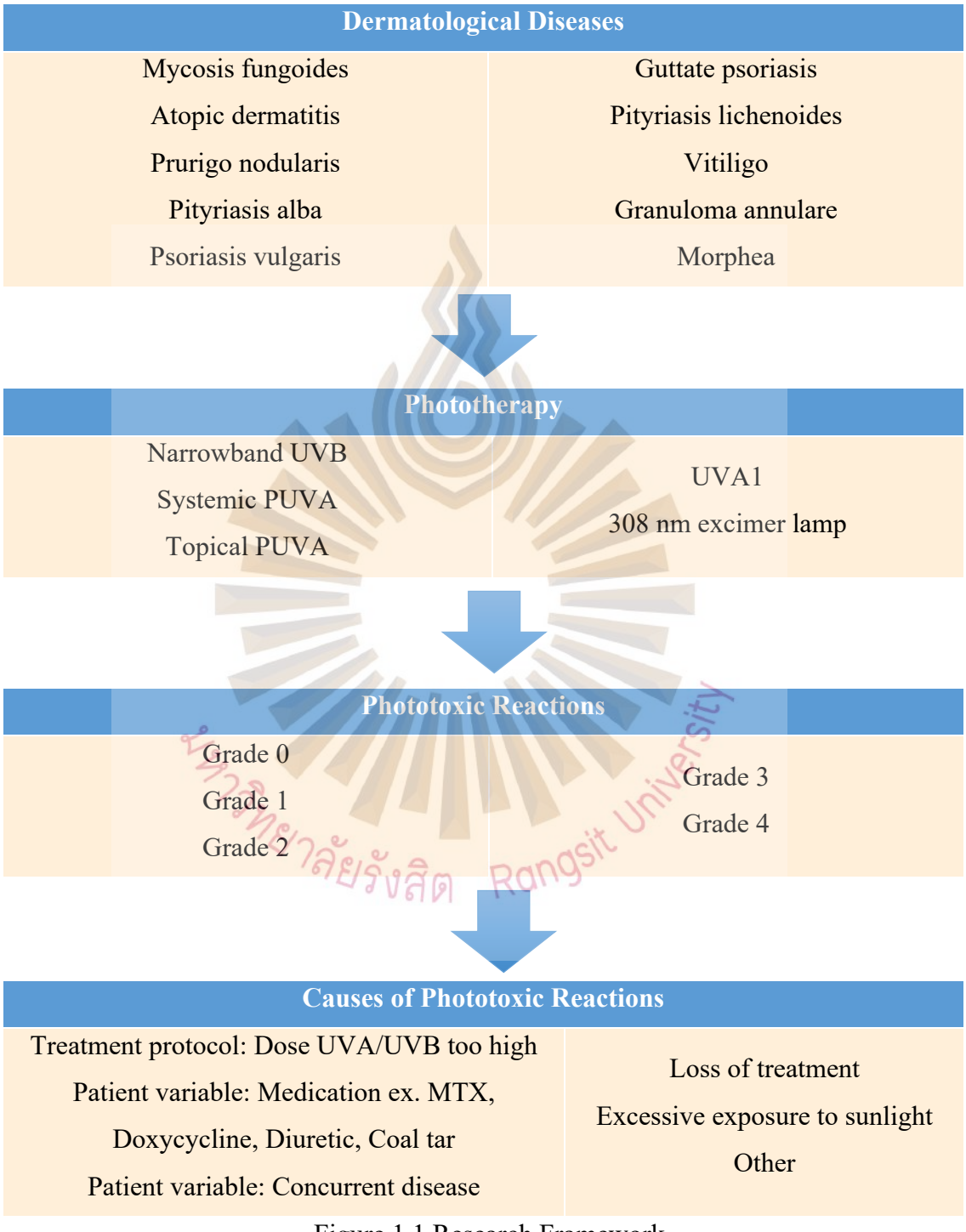

Figure 1.1 Research Framework

1.5 Definition of Terms

Phototherapy A specialized medical intervention employing ultraviolet (UV) radiation as a therapeutic tool for many dermatological conditions. Diseases like psoriasis, vitiligo, and atopic dermatitis, among others, can be significantly alleviated through this treatment. The modes of phototherapy are vast and technologically advanced, embracing spectrums from broadband UVB, which spans 290-230 nm, to the precision of the 308 nm excimer laser. UVA radiation, both in the range of 340-400 nm (UVA1) and 320-400 nm, plays its role too. Especially intriguing is the combination therapy of UVA with psoralens, termed as PUVA, which offers unique therapeutic advantages by harnessing both properties.

Phototoxic reaction At its core, it involves certain medications or topical agents that, under usual circumstances, are inert. However, upon exposure to specific light wavelengths, these agents undergo activation, causing cellular harm. This light-induced cellular damage can happen to anyone with the drug in their system and exposed to the triggering light. The universality of this reaction, devoid of predisposing genetic or immunological factors, makes it distinct from photoallergic reactions.

Narrowband UVB There are two primary contenders. Broadband UVB therapy uses a wide UV spectrum that ranges between 280 and 320 nm. In contrast, narrowband UVB therapy is more focused and employs a sliver of that spectrum, specifically around the 311 nm mark, often referred to as UVB 311. This specificity is believed to offer targeted therapeutic benefits while minimizing potential side effects.

Excimer lamp Stands out in its unique light emission characteristics. Emitting a monochromatic light at 308 nm, this lamp owes its properties to the combination of xenon and chlorine gases. The resultant light is useful in various dermatological applications, offering targeted treatment advantages.

Psoralen plus UVA PUVA is a testament to the therapeutic might of combination therapies. It merges the photoreactive properties of a group of compounds called psoralens with the penetrating ability of UVA radiation. On their own, either might not offer much, but together, they produce a potent phototoxic effect that is beneficial in treating certain skin conditions. The flexibility in administering psoralens—whether orally ingested or topically applied through solutions, creams, or baths—adds to the versatility of PUVA therapy, tailoring the treatment to individual patient needs.

Chapter 2

Literature Review

Phototherapy is the application of ultraviolet (UV) radiation to treat dermatological diseases. However, phototoxicity is one of the adverse effects (AEs) of phototherapy. Phototoxicities included prickling, burning, sunburn exacerbation, blistering, hyperpigmentation, photo-onycholysis, skin fragility, and telangiectasia. UV overdose, sun exposure period, light skin phototype, phototoxic substances, medicines, and the environment can all induce phototoxicity (Henry, 2019; Martin, Laube, Edwards, Gambles, & Anstey, 2007; Belinchón et al., 2020; Vázquez-Osorio, González-Delgado, Suárez-García, Gonzalvo-Rodríguez, & Rodríguez-Díaz, 2018; Ibbotson, 2018). Older patients, whose polypharmacy frequently includes photoactive medicines, are thus at a greater risk for developing photosensitivity produced by pharmaceuticals (Ibbotson, & Dawe, 2016).

The selection of phototherapy modality depends on dermatological conditions. Currently widely used ultraviolet (UV) radiation; Broadband UVB (290-230 nm), Narrowband UVB (311-313 nm), UVA1 (340-400 nm), and Psoralen plus UVA (PUVA); for treating dermatological diseases in the whole body or localized lesion. 308-nm Excimer laser is most useful in the treatment of limited areas.

Figure 2.1 Phototherapy: Whole body Cabinet

Source: Pattamadilok, 2022

Figure 2.2 Localized Phototherapy

Source: Pattamadilok, 2022

Targeted Phototherapy

Figure 2.3 Phototherapy Modality

Source: Pattamadilok, 2022

2.1 Drug-Induced Photosensitivity

Drug-induced photosensitivity refers to a prevalent dermatological adverse reaction that emerges from the interplay between specific drugs and ultraviolet radiation, predominantly ultraviolet A (UVA). The manifestations of this phenomenon are twofold: phototoxicity and photoallergy. Phototoxic reactions occur when topical and systemic drugs or their subsequent metabolites absorb light, resulting in

immediate cellular damage. Such reactions can manifest in any individual, provided there's adequate exposure to both the drug (or its metabolite) and the relevant wavelengths of radiation. Conversely, photoallergic reactions represent a delayed type IV hypersensitivity response. This reaction occurs after the absorption of photons by specific molecules, necessitating a sensitization phase. Only individuals previously sensitized to the photoallergen can exhibit this reaction, which arises even from minimal allergen concentrations. Clinically distinguishing between the two, phototoxicity presents rapidly, resembling an intensified sunburn, while a protracted eczematous reaction marks photoallergy. The clinical presentations of drug-induced photosensitivity can be varied, as outlined by Di Bartolomeo et al. (2022).

2.1.1 Clinical Characteristics

Systemic drug photosensitivity predominantly manifests in two primary forms: an intensified sunburn reaction or an acute eczematous response, both of which are localized to areas exposed to sunlight. However, its clinical spectrum is broad, with other possible presentations including urticaria, lichenoid eruptions, telangiectasia, subacute cutaneous lupus erythematosus (LE), formation of bullae, post-inflammatory hyperpigmentation, lesions resembling vitiligo, and even non-melanoma skin cancers (Refer to Table 2.1 for a comprehensive list).

Table 2.1 Clinical Photosensitivity Patterns Mostly involve Phototoxicity, Photoallergy, or other Immune-Mediated Reactions.

Phototoxicity	Immune-Mediated Reactions
Exaggerated “sunburn”	Urticaria
Pseudoporphyria	Acute or subacute eczema
Photo-onycholysis	Erythema multiform-like
Hyperpigmentation	Lichenoid reactions
Hypopigmentation (vitiligo-like lesions)	Subacute/chronic lupus erythematosus
Telangiectasia	
Purpura	
Pellagra-like reactions	

Table 2.1 Clinical Photosensitivity Patterns mostly involve Phototoxicity, Photoallergy, or other Immune-Mediated Reactions. (Cont.)

Phototoxicity	Immune-Mediated Reactions
Actinic keratosis and skin cancer Accelerated photoaging	

Source: Pereira, Xará, & Gonçalo, 2022

Directly after sun exposure, skin responses such as those seen with vemurafenib-induced photosensitivity can arise. Most phototoxic or photoallergic skin reactions might appear within a day or two, while other answers like pseudoporphyria, photo-onycholysis, or subacute cutaneous LE might take days or weeks to emerge. Some effects, especially those related to skin aging and certain skin cancers due to photoactive drug interactions, might be seen after several years.

Predominantly, the systemic drug photosensitivity reaction is observed on the face, specifically the forehead, extending to the V-region of the neck and chest and on the back of the hands and forearms, generally following a symmetrical pattern. Typically, areas shaded on the face, including the upper eyelids, upper lip, and deep facial creases, remain unaffected. Similarly, regions like behind the ears, under the chin, or areas concealed by facial hair also remain untouched. Ample bodily folds and parts covered by attire or accessories also generally remain unscathed (Pereira et al., 2022).

2.1.1.1 Acute Photosensitivity Manifestations

Acute photoallergy due to systemic medications often presents as patches of eczema, either merging or separate, in sunlit areas, though sometimes they may look like erythema multiforme.

Most acute phototoxic reactions manifest between 12 to 24 hours post-sun exposure and mimic an intense sunburn. The initial sharply defined redness can progress into fluid-filled or more prominent blisters, eventually leading to large-

scale epidermal shedding. Persistent skin darkening is a common aftermath (Gouveia, Gameiro, Coutinho, & Gonçalo, 2016).

2.1.1.2 Subacute Drug Photosensitivity Manifestations

These reactions usually emerge over days to weeks and are generally attributed to phototoxic mechanisms, as in pseudoporphyria, photoonycolysis, skin discoloration, telangiectasia, and purpura. Conversely, ring-shaped lesions might be indicative of drug-induced subacute cutaneous LE.

2.1.1.3 Delayed and Late Effects of Photosensitivity

Chronic exposure to photo-reactive drugs can lead to rapid skin aging, actinic keratosis, and skin cancers. This is possibly due to the photogenotoxic effects of certain medications. Excluding psoralens, which after PUVA treatment are linked with a dose-related increased skin cancer risk, certain drugs like naproxen, chlorpromazine, and specific fluoroquinolones augment UV-induced DNA damage in lab settings and escalate epidermal tumors in animal studies. In people, drugs that might cause photosensitivity, like diuretics and cardiovascular medicines, have been increasingly linked with precancerous skin growths. Recent findings also suggest that brief exposure (spanning weeks or months) to drugs like voriconazole or vemurafenib, and prolonged exposure to diuretics and antihypertensive medications, heightens the risk of non-melanoma skin cancers and possibly melanoma (Pereira et al., 2022; Gouveia et al., 2016).

2.1.2 Principal Medications Inducing Photosensitivity

The list of topical and systemic drugs known to cause photosensitivity is ever-growing, cutting across multiple pharmacological groups. Prominently, photosensitivity has been noted with NSAIDs, antimicrobials like tetracyclines, fluoroquinolones, sulphonamides, and with psychotropic, cardiovascular, and anti-cancer drugs (Pereira et al., 2022; Gouveia et al., 2016). (Table 2.2).

2.2 Fundamentals of Drug Photosensitivity Treatment

The primary steps in addressing drug photosensitivity are ceasing the drug in question and evading sun exposure. If the medication is crucial, lacks a viable substitute, or the replacement drug is not as effective, strategies such as sun avoidance, using protective wear, and applying a broad-spectrum sunscreen effective against UVA might be sufficient to alleviate photosensitivity. This protective quality of sunscreens is particularly noticeable in phototoxic reactions, as evidenced in the cases of voriconazole, vemurafenib, and amiodarone.

Using a broad-spectrum sunscreen can also be a proactive approach when starting a drug known to cause photosensitivity. Still, it's essential to know that chemical UV filters are a notable cause of contact photosensitivity, especially in individuals with prior skin conditions.

For instances of acute photoallergy, merely discontinuing the offending drug and avoiding the sun might not provide immediate relief from skin lesions, necessitating more proactive treatment. Applying topical corticosteroids for a limited duration might be advised, and intense reactions might require a brief regimen of oral corticosteroids with rapid dose reduction.

Acute phototoxic reactions, primarily manifesting as intense sunburns, can benefit from moisturizing agents and sun protection, even post-reaction. The effectiveness of corticosteroids in these cases is a topic of debate (Gouveia et al., 2016).

Table 2.2 Main Drugs Causing Photosensitivity

Systemic Photosensitivity		Topical Photosensitivity
Antimicrobials	Antidepressants	NSAIDs
Tetracyclines[a] (doxycycline, minocycline)	Clomipramine, Imipramine, Sertraline	Ketoprofen[c]
		Piroxicam[c], Etofenamate[c]
		Piroxicam[c], Etofenamate[c] Benzydamine
		Diclofenac
Sulphonamides (sulfamethoxazole)	Cardiovascular drugs	Phenothiazines
Fluoroquinolones (lomefloxacin, ciprofloxacin)[a]	Amiodarone[a], quinidine	Chlorpromazine
		Promethazine, Chlorhydrate Chlorproethazine
Voriconazole[a,b]	Furosemide, Torasemide and Thiazide Diuretics	Plants (used as drugs)
Terbinafine, Griseofulvina	Anti-cancer Agents	Ruta Graveola (common rue)
Efavirenz, Tenofovir, Faldeprevir	Paclitaxel, Docetaxel	Photodynamic Therapy Agents
NSAIDs	Methotrexate, 5-fluoracil	5-aminolevulinic acid
Arylpropionic acids: Tiaprofenic acid[a], Suprofen Naproxen, Ibuprofen, Ibuproxam, Carprofen[a]	Dacarbazine	
	Miscellaneous	
	Psoralens[b], Fenofibrate, Simvastatin	
Piroxicam[c,d]	Sulfonylureas, Sitagliptin, Metformin	
Celecoxib, Diclofenac[d]	Flutamide, Finasteride, Pirfenidone	

Table 2.2 Main Drugs Causing Photosensitivity (Cont.)

Systemic Photosensitivity		Topical Photosensitivity
NSAIDs	Miscellaneous	
Azapropazone, Phenylbutazone, Indomethacin	Retinoids	
Phenothiazines	Plants (used as drugs)[a]	
Chlorpromazine[d], Thioridazine	Hypericum Perforatum (St. John's wort)	
Targeted therapies	Kava extracts	
Vemurafenib[b], Imatinib, Vandetanib		

[a]Mainly phototoxic. [b]An increase of NMSC and actinic keratosis. [c]Mainly photoallergic. [d]Often also from topical or airborne exposure, mainly in occupational settings.

Source: Pereira et al., 2022

2.3 Phototherapy for Psoriasis

Numerous research efforts have underscored the heightened effectiveness of PUVA over NB-UVB in managing plaque-type psoriasis (Singer & Berneburg, 2018; Elmets et al., 2020; Armstrong & Read, 2020; Almutawa, Alnomair, Wang, Hamzavi & Lim, 2013; Chen, Yang, Cheng, Liu & Zhang, 2013). Based on findings related to clearance, some studies indicate PUVA's superiority over NB-UVB, with BB-UVB and bath PUVA following in terms of effectiveness (Almutawa et al., 2013). However other research efforts haven't identified a definitive statistical disparity in clearance rates between PUVA and NB-UVB. Many point to swifter skin clearance using PUVA, albeit with heightened side effects.

Even with oral PUVA's pronounced effectiveness in handling psoriasis compared to UV-B, it's becoming less favored because of the heightened risk of skin cancer with prolonged usage. NB-UVB emerges as a more appealing option than oral or bath PUVA owing to its convenience, absence of psoralen necessity, better accessibility, and reduced phototoxicity or carcinogenic potential. Furthermore, studies have emphasized that NB-UVB does not adversely impact pregnant women or Asian children (Singer & Berneburg, 2018; Elmets et al., 2020; Armstrong & Read, 2020; Chen et al., 2013; Van et al., 2019; Stern, 2012; Kemény, Varga, & Novak, 2019). UV-B's side effects encompass issues like erythema, itchiness, blistering, accelerated skin aging, and increased chances of skin cancer, whereas PUVA might result in gastrointestinal disturbances, burning sensations, itchiness, excessive hair growth, and photoaging (Singer & Berneburg, 2018; Armstrong & Read, 2020; Almutawa et al., 2013).

The 308-nm Excimer laser is most effective for milder psoriasis cases when treating confined areas, specifically covering less than 10% of the body surface. This includes skin folds, palms, soles, and areas like elbows, knees, and ankles, as well as lesions resulting from the Koebner phenomenon or plaques resistant to treatment (Kemény, Varga, & Novak, 2019; Matos, Ling, & Sheth, 2016).

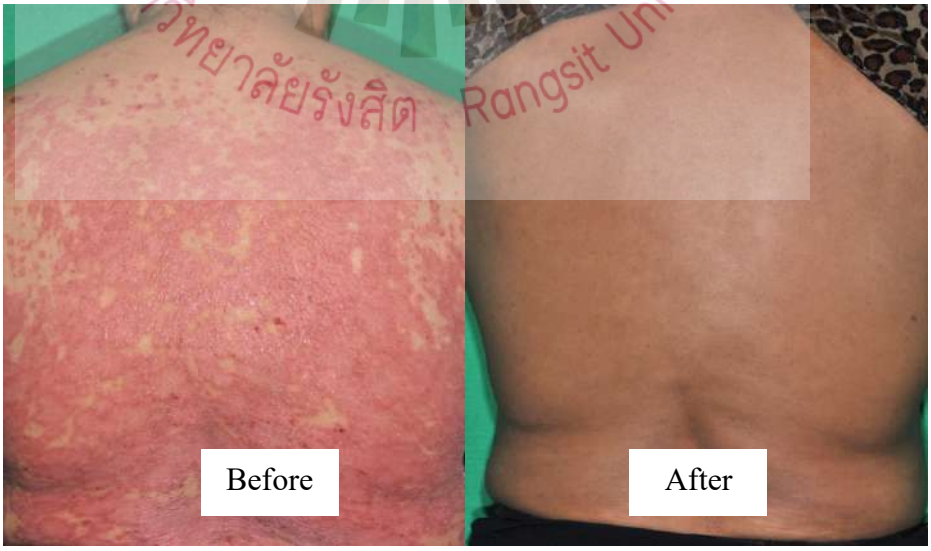

Figure 2.4 NB-UVB phototherapy in Psoriasis vulgaris

Source: Pattamadilok, 2022

2.4 Phototherapy for Vitiligo

Emerging evidence from numerous studies indicates that, in treating vitiligo for adults and children, NB-UVB offers superior results and has fewer side effects than oral PUVA.

As a result of consistent findings highlighting the heightened efficacy of NB-UVB relative to other phototherapeutic methods, it has been established as the primary treatment approach for widespread vitiligo. Beyond its effectiveness, the safety profile of NB-UVB stands out, especially when juxtaposed with PUVA. This enhanced safety is primarily attributed to omitting psoralen-related side effects (Thu et al., 2019; Bae et al., 2017; Esmat et al., 2017). It's worth noting that the most promising treatment outcomes with NB-UVB are generally observed in facial and neck regions, while the extremities, like hands and feet, tend to have a subdued response (Esmat et al., 2017).

Interestingly, Hong, Park, and Lee (2005) found that excimer lasers outperformed NB-UVB in vitiligo treatment efficacy. Furthermore, several contemporary meta-analyses have drawn parallels in the efficacy levels between excimer light, excimer laser, and NB-UVB in vitiligo treatment (Esmat et al., 2017).

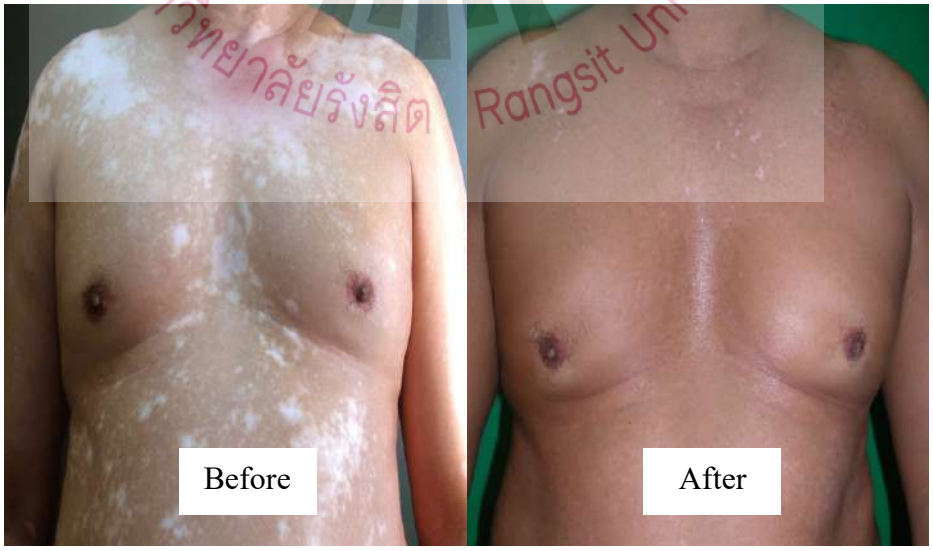

Figure 2.5 NB-UVB Phototherapy in Vitiligo

Source: Pattamadilok, 2022

2.5 Phototherapy for Atopic dermatitis

In the management of Atopic dermatitis, phototherapy emerges as a secondary option when primary treatments—like emollients, topical corticosteroids, and topical calcineurin inhibitors—don't yield the desired results (Rodenbeck, Silverberg, & Silverberg, 2016).

Multiple studies indicate that NB-UVB offers superior results compared to UVA-1 in terms of improving AD severity. Yet, some research suggests no meaningful statistical difference between the efficacies of UVA-1 and NB-UVB treatments (Ortiz-Salvador, & Pérez-Ferriols, 2017).

In treating AD, NB-UVB and medium-dose UVA-1 phototherapy have shown the most promising results (Rodenbeck, Silverberg, & Silverberg, 2016; Ortiz-Salvador, & Pérez-Ferriols, 2017). NB-UVB seems the preferred treatment for chronic AD conditions, whereas UVA-1 can be an effective solution for acute outbreaks. The modern versions of the Goeckerman regimen, which combine coal tar with BBUVB, have been deemed effective for more severe AD cases. However, concerns regarding the potential carcinogenic effects of coal tar have dampened its widespread adoption. In persistent, localized AD lesions, the Excimer laser (308 nm) has emerged as a viable option. Moreover, the safety of employing NBUVB in pediatric patients has been established through extensive documentation (Ortiz-Salvador, & Pérez-Ferriols, 2017).

2.6 Utilizing Narrowband Ultraviolet B Phototherapy for Plaque type Psoriasis

Establishing the minimal erythema dose (MED) involves exposing a series of six 1-cm^2 patches of skin, typically located on the inner side of the forearm or the lower back, to incrementally increasing intensities of UV radiation. This radiation stems from the same equipment set to be used for phototherapy. After 24 hours, the areas exposed to UV radiation are inspected. Phototherapy then commences, typically

at a level ranging between 35% and 70% of the smallest UV dosage, resulting in consistent erythema across the entire exposed section.

An alternative method to set the initial phototherapy dose hinges on the patient's Fitzpatrick skin phototype, as detailed in Table 2.3 Following treatments are then typically scheduled 2 to 5 times weekly. Each session sees a dose increase unless the patient exhibits an erythema response. In instances where an erythema reaction is observed, it's advised to either reduce the treatment intensity or postpone the session altogether, as outlined in Tables 2.3 and 2.6.

In scenarios where all 24 NB-UVB lamps are replaced simultaneously, the dose should be lowered by approximately 30% from the last known value. Subsequent treatments should then see a cautious increase in the dose in line with prior increments. For those on a maintenance regimen, the dose should be upped by around 10% each session until the previous dose is reattained.

2.7 Implementing Oral Psoralen and Ultraviolet A Phototherapy for Psoriasis and Vitiligo

When combined with ultraviolet A radiation (UVA), Psoralen forms the basis of PUVA therapy, a well-established regimen for treating conditions like psoriasis and vitiligo. This treatment capitalizes on the photosensitizing properties of psoralen, enhancing the skin's sensitivity to UVA radiation and facilitating targeted therapy.

Three distinct psoralen derivatives can be employed in PUVA:

1) 8-methoxypsoralen (8-MOP),

2) 5-methoxypsoralen (5-MOP), and

3) 4,5′,8-trimethylpsoralen.

Of these, only 8-MOP is available in Thailand. The oral formulation of 8-MOP is usually prescribed at a concentration of 0.5-0.6 mg/kg, and it's taken approximately 1 to 2 hours before UVA exposure to ensure optimal photosensitization.

The initiation dose for oral PUVA therapy's UVA radiation typically aligns with the patient's skin phototype or is set between 50% and 70% of the minimum phototoxic dose, as outlined in Table 2.4. This minimum phototoxic dose is derived by administering the patient with the intended oral psoralen dosage for the PUVA therapy and exposing six distinct 1-cm^2 skin patches to progressive doses of UVA. The evaluation of this dose happens 72 hours after the UVA exposure. This dosage represents the most minor UVA exposure that induces consistent erythema throughout the exposed section.

PUVA treatments are traditionally scheduled 2 to 3 times weekly, ensuring no back-to-back sessions. Each treatment sees an incremental increase in UVA exposure. However, this dose may be altered based on observed erythema responses or if sessions are missed, with specifics provided in Table 2.4.

2.8 Implementing Topical Psoralen and Ultraviolet A Phototherapy for Psoriasis and Vitiligo

Topical PUVA therapy employs psoralen in a topical form, specifically 8-methoxy psoralen (8-MOP), before exposure to UVA radiation. The main advantage of topical forms is the targeted delivery of psoralen to the areas of concern.

Available Formats:

1) Creams
2) Ointments
3) Lotions

(Refer to Table 2.5 for specific formulations and concentrations.)

However, there are notable considerations: It can result in uneven skin treatment, phototoxic reactions, and irregular patches of hyperpigmentation. An application can be labor-intensive.

Given these challenges, topical psoralens are more strategically employed for localized conditions. They are especially favored in limited plaque psoriasis and palmoplantar psoriasis due to their ability to target and treat specific problematic areas without systemic effects.

Ensuring proper and uniform application and strictly following the UVA exposure guidelines is essential for optimal results. Furthermore, patients should be monitored regularly for any adverse effects and to assess the therapy's efficacy.

Table 2.3 Narrowband Ultraviolet B Phototherapy for Plaque type Psoriasis

Narrowband Ultraviolet B Phototherapy
1) MED based a) MED determination Expose 1-cm^2 areas on the lower back or inner aspect of the forearm to 200, 400, 600, 800, 1000, 1200 mJ/cm^2; read at 24 hours b) Initial exposure: 35, 50 or 70% of MED c) Subsequent exposures: 2 to 5 times per week Increase UV dose by 20% per treatment for 2-4 weeks then increase 10% per treatment d) No increment if present of mild erythema is observed, then maintenance in the same dose 2) Skin phototype based: a) In case MED cannot be obtained and maximum dose, using the average MED of Thai people skin b) Initial exposure based on Fitzpatrick skin phototype; subsequent exposures as above

* MED, minimal erythema dose; NB-UVB, narrowband ultraviolet B.

Table 2.3 Narrowband Ultraviolet B Phototherapy for Plaque type Psoriasis (Cont.)

Narrowband Ultraviolet B Phototherapy		
Skin type	MED (mJ/cm^2)	Maximum Dose (mJ/cm^2)
III	410	800
IV	570	2,000
V	800	2,500

Modified from the Institute of Dermatology, Thailand.

Source: Pattamadilok, 2022

Table 2.4 Oral Psoralen and Ultraviolet A Photochemotherapy

Oral Psoralen and Ultraviolet A Photochemotherapy
1) Psoralen dose Meladinine 0.5-0.6 mg/Kg (maximum 70 mg); 60-120 minutes before UVA MPD based a) MPD determination Expose 1-cm^2 areas on the lower back or inner aspect of the forearm to 0.5, 1, 2, 3, 4, 5 J/cm2 UVA; read 72 hours after UVA exposure b) Initial exposure: 50 to 70% of MPD c) Subsequent exposures: 2 to 3 times per week d) Increment dose Treatment 1-30: increase 0.5-1.5 J/cm^2 If clinical improved, then maintenance in the same dose 2) Skin phototype based: a) Initial exposure based on Fitzpatrick skin phototype; subsequent exposures as above b) Maximum dose Body; 12 J/cm^2 (skin phototype III, IV) 20 J/cm^2 (skin phototype V, VI) Face; 4 J/cm^2

Table 2.4 Oral Psoralen and Ultraviolet A Photochemotherapy (Cont.)

Oral Psoralen and Ultraviolet A Photochemotherapy			
Systemic PUVA	Dose of Treatment in J/cm^2		
	For Psoriasis	For Vitiligo	Other Diseases
Initial Dose	Skin phototype III 3.5 J/cm^2 Skin phototype IV 3.5-4.5 J/cm^2	1 J/cm^2	Skin phototype III 3.5 J/cm^2 Skin phototype IV 4.5 J/cm^2
Increment dose	1 J/cm^2/Rx	0.5 J/cm^2/Rx	1 J/cm^2/Rx

* MPD, minimal phototoxic dose; PUVA, psoralen, and ultraviolet A; UVA, ultraviolet A. Modified from the Institute of Dermatology, Thailand.

Source: Pattamadilok, 2022

Table 2.5 Topical Psoralen and Ultraviolet A Photochemotherapy

Topical Psoralen and Ultraviolet A Photochemotherapy **Topical Meladinine 0.05%, 0.025%**	
Topical PUVA	UVA Dose of Treatment in J/cm^2
Initial dose	0.3-0.5 J/cm^2
Increment dose	0.3-0.5 J/cm^2/Rx

Modified from the Institute of Dermatology, Thailand.

Source: Pattamadilok, 2022

Table 2.6 Modification of Phototherapy Dose for Phototoxic Reaction or Missed Sessions

Modification of Phototherapy Dose for Phototoxic Reaction or Missed Sessions	
Phototoxic grading	Modification of dose
Grade I Mild perceptible erythema	Next dose = the same dose After that, follow the incremental regimen

Table 2.6 Modification of Phototherapy Dose for Phototoxic Reaction or Missed Sessions (Cont.)

Modification of Phototherapy Dose for Phototoxic Reaction or Missed Sessions	
Phototoxic grading	Modification of dose
Grade II Asymptomatic well-defined erythema	Postpone treatment until erythema is resolved. Next dose = 30% of the burning dose After that, follow the incremental regimen
Grade III Symptomatic erythema	Postpone treatment until erythema is resolved. Next dose = 50% of the burning dose After that, follow the incremental regimen
Grade IV Severe erythema with edema, blister	Postpone treatment until erythema is resolved. Next dose = 50% of the burning dose After that, follow the incremental regimen
Modification of Phototherapy Dose for Missed Treatments	
< 1 week	No increase in dose
1 to 2 weeks	Decrease dose by 50% (BB-UVB) or 25% (NB-UVB or PUVA)
2 to 3 weeks	Decrease dose by 75% (BB-UVB) or 50% (NB-UVB or PUVA)
> 3 weeks	Restart at the initial exposure dose

Modified from the Institute of Dermatology, Thailand.

Source: Pattamadilok, 2022

Table 2.6 specifies the UVB or UVA dose adjustments in the event of a burn reaction during phototherapy. A burn reported by the patient at the next visit, even if no longer visible, should be managed in the same manner as a still visible reaction. Burns over limited body areas, such as the face or breasts, can be controlled by local application of an appropriate sunscreen before or through subsequent treatments, which is significant if the area is not affected by the disease being treated.

Photosensitivity induced by drugs encompasses both phototoxicity and photoallergy. Phototoxicity is characterized by an immediate response, resembling an intensified sunburn, exhibited upon exposure to a phototoxic agent and UV radiation. On the other hand, photoallergy manifests as a delayed eczematous reaction, and it is an immunological response to chemicals modified by UVA, with commonly implicated agents including topical sunscreens and antimicrobials in the U.S. and the U.K., and topical nonsteroidal anti-inflammatory agents in Europe.

Skin color variations primarily arise from the differential quantity and distribution of melanin among epidermal melanocytes and keratinocytes rather than the sheer number of melanocytes (High, Tomasini, Argenziano, & Zalaudek, 2018). The Fitzpatrick skin phototype classification elucidates the different phototypes (I-VI) and their respective responses to Ultraviolet radiation. In reaction to UV-R exposure, the skin develops two protective barriers: an increased stratum corneum thickness and an intensified melanin filter in epidermal cells (Costin, & Hearing, 2007). As an efficient UV barrier, pigmented skin significantly minimizes sunburn reactions. As a result, increased UV radiation doses tend to be more effective and better tolerated by darker skin (Ware, Guiyab, & Okoye, 2020). Nonetheless, this pigmentation level also profoundly influences melanin production, known as tanning.

Tanning, an elevation of skin pigmentation beyond its basal level, is physiologically induced by UV-R. The process of UV-driven skin darkening encompasses an increase in melanocyte numbers, augmented melanin synthesis, and enhanced melanocyte dendricity—this last factor being integral to melanin's transfer to keratinocytes.

The tanning response has been demonstrated to undergo two unique phases: immediate pigment darkening and delayed tanning. Genetic factors primarily determine both phases and are markedly pronounced in individuals with inherently dark pigmentation (High et al., 2018; Costin, & Hearing, 2007). Martin et al. (2007) noted that acute adverse events across all phototherapy treatments exceeded 0.8%.

Belinchon et al. (2020) documented that the incidence rate of adverse events (AEs) linked with phototherapy stood at 19.1%, broken down into NBUVB (18.1%), topical PUVA (16.1%), and systemic PUVA (32.5%). The AEs encompassed erythema, hyperpigmentation, pruritus, UV burn, phototoxicity, pain, cutaneous lupus, and gastrointestinal symptoms. Specific conditions like palmoplantar psoriasis, mycosis fungoides, hand eczema, and pityriasis lichenoides exhibited heightened treatment interruption rates due to AEs.

Other studies have indicated phototoxicity rates of 10.9% associated with PUVA, with protocol issues cited as the primary cause (Morison, Marwaha, & Beck, 1997). Such reactions are more prevalent in individuals with lighter skin phototypes (I and II) (Vazquez et al., 2018). Past studies have shown AE rates with NB-UVB ranging from 10% to 94% (Ibbotson et al., 2004; Green, Ferguson, Lakshmipathi, & Johnson, 1988; Coven, Burack, Gilleaudeau, Keogh, Ozawa, & Krueger, 1997; Gordon et al., 1999; Green, Lakshmipathi, Johnson, & Ferguson, 1992).

Elderly individuals, often subjected to polypharmacy, including photoactive drugs, are consequently more susceptible to drug-induced photosensitivity (Ibbotson, 2018). Phototoxic reactions, backed by robust evidence, have been linked to vemurafenib, nonsteroidal anti-inflammatory drugs, and certain antibiotics, particularly fluoroquinolones and tetracyclines. The most recurrently reported drugs inducing phototoxicity include vemurafenib, voriconazole, doxycycline, hydrochlorothiazide, amiodarone, and chlorpromazine (Kim et al., 2018).

Even though phototherapy remains a primary therapeutic approach, there is a shortage of studies exploring factors associated with phototoxic reactions in phototherapy-treated patients, especially in sun-rich regions like Thailand. A more in-depth understanding of causative factors for phototoxic reactions in patients can equip physicians to make better therapeutic decisions, possibly averting phototoxic reactions.

Chapter 3

Research Methodology

3.1 Population and Samples

3.1.1 Target Populations

Males and females in all age ranges were diagnosed with phototoxicities due to phototherapy by the Radiobiology Department of the Institute of Dermatology, Thailand (2016-2020).

3.1.2 Sample Size

A total of 200 patients were recruited for this study, using the formula for estimating an infinite population proportion:

Formula $$n = \frac{z^2_{1-\frac{\alpha}{2}}\, p(1-p)}{d^2} \qquad (3\text{-}1)$$

Reference: Wayne, (1995). Biostatistics: A Foundation of Analysis in the Health Sciences (6th ed.). John Wiley & Sons, Inc., 180.

Usage: n = sample size

p = the proportion of events in an outcome from a previous or similar study

d = the maximum tolerated error determined by the investigator

$Z_{1-\alpha/2}$ = 1.96 ($\alpha = 0.05$)

alpha (α) = depends on the confidence level (1- α)

Using the number of p = 0.19 from the report of Isabel Belinchon (Belinchon et al., 2020), at a 95% confidence interval (CI), with d = 6%

Formula; $$n = \frac{z^2_{1-\frac{\alpha}{2}} p(1-p)}{d^2}$$

Represent; P = 0.19, Z = 1.96, d = 0.06

; $$n = \frac{(1.96)^2 (0.19) (1-0.19)}{(0.06)^2}$$

; n = 165 subjects

3.2 Research Instruments

We collected data from all patients who attended the Photodermatology unit, the Institute of Dermatology, Bangkok, Thailand, from October 2015 to September 2020. Treatments included in the study were NB-UVB, systemic PUVA, topical PUVA, ultraviolet A (UVA), and 308 nm excimer lamp.

The following information was collected retrospectively: dermatological disease being treated, sex, age, occupation, exposure time to sunlight (indoor/ outdoor worker), season (summer/ rainy/ winter), Fitzpatrick skin type, underlying diseases (if any), current medications during phototherapy, phototherapy modality, start dose/ increment dose, current cycle, phototoxic dose, total cumulative dose, level of phototoxicity (grade 0-4), location of phototoxicity, causes of phototoxicity and its impact on treatment discontinuation (yes/no). The levels of phototoxic reactions considered were: grade 0 (defined as severe generalized itching, burning sensation, no erythema), grade 1 (defined as minimal perceptible erythema), grade 2 (defined as well-defined asymptomatic erythema), grade 3 (defined as symptomatic erythema persisting more than 24 hours), grade 4 (defined as severe erythema with edema, blister). The causes of phototoxic reactions were: Treatment protocol (dose UVA/UVB too high), patient variable (Medication ex. MTX, Doxycycline, Diuretic, Coal tar), concurrent disease, loss treatment, excessive exposure to sunlight, and others. The

reasons for stopping treatment were categorized as the patient's decision, lack of efficacy (no response or worsening of cutaneous lesions), or adverse events (AEs).

The local research ethics committee approved the study protocol. The study was performed according to the Declaration of Helsinki.

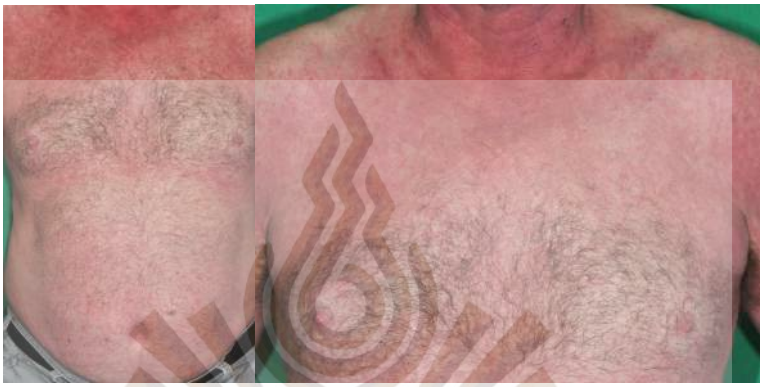

Figure 3.1 Phototoxic Reaction Grade 3
(defined as symptomatic erythema persisting for more than 24 hours)

Phototoxic Reaction Grade 4 (severe erythema with edema, blister).

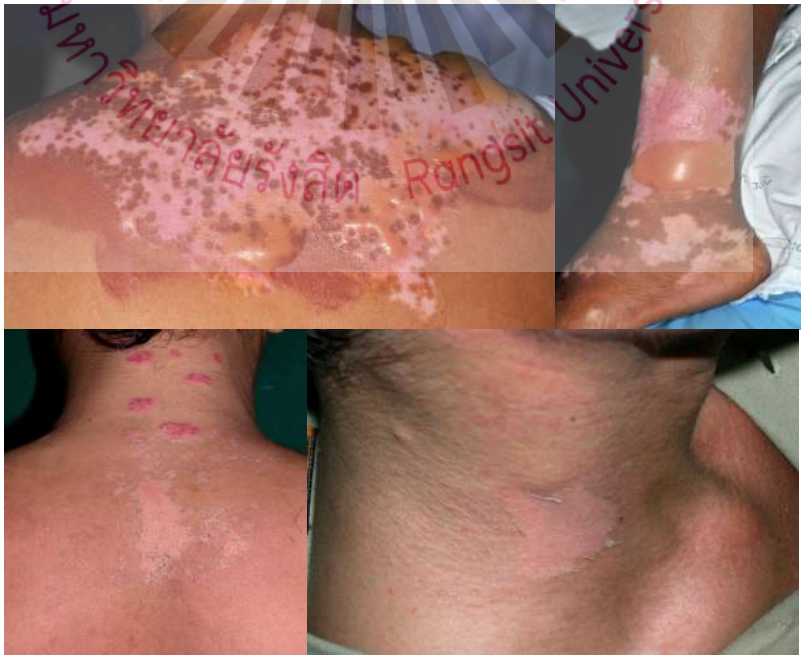

Figure 3.2 Phototoxic Reaction Grades 3 and 4
Source: Pattamadilok, 2022

3.2.1 Record form

Case Record Form

Case No. .....

Diagnosis	☐ C84.0 Mycosis fungoides ☐ L20.9 Atopic dermatitis, unspecified ☐ L28.1 Prurigo nodularis ☐ L30.5 Pityriasis alba ☐ L40.0 Psoriasis vulgaris ☐ L40.4 Guttate psoriasis ☐ L41.0 Pityriasis lichenoides et varioliformis acuta	☐ L41.1 Pityriasis lichenoides chronica ☐ L57.8 Other skin changes due to chronic exposure to nonionizing radiation ☐ L80 Vitiligo ☐ L92.0 Granuloma annulare ☐ L94.0 Localized scleroderma [morphea] ☐ Others.....
Sex	☐ Male	☐ Female
Age (years)		
Occupation		
Expose time to sunlight	☐ Indoor worker	☐ Outdoor worker
Seasons	☐ Summer (Mid February – Mid May) ☐ Rainy (Mid May – October)	☐ Winter (Mid October - Mid February)
Skin Type	☐ I ☐ II ☐ III ☐ IV ☐ V ☐ VI	
Underlying diseases	☐ Diabetes mellitus ☐ Thyroid disease ☐ Photodermatoses ☐ Hypertension ☐ Autoimmune diseases: Lab ANA..... ☐ Others.....	☐ Dyslipidemia
Current Medications during phototherapy (include herbal use and vitamin)		

Figure 3.3 Case Record Form

Case Record Form

Case No. …...

Phototherapy Modality	Location of Phototoxic	Start Dose (J/cm^2) / Increment dose (%)	Current Cycle	Phototoxic Dose (J/cm^2)	Total Cumulative Dose (J/cm^2)	Level of Phototoxic (Grade 0-4) *					Causes of Phototoxic **	Discontinuation of Phototherapy
						0	1	2	3	4		
☐ Narrowband UVB ☐ Systemic PUVA ☐ Topical PUVA ☐ Meladinine 0.025% ☐ Meladinine 0.05% ☐ UVA1 ☐ 308 nm excimer lamp	☐ Whole body ☐ Localized …… ☐ Targeted - DuaLight ……					☐	☐	☐	☐	☐	☐ TP ☐ PM ☐ PD ☐ LT ☐ ES ☐ O	☐ Yes ☐ No
						☐ Photo-onycholysis ☐ Lentigines						

*Level of Phototoxic

Grade 0 = Severe generalized itching, burning sensation, no erythema

Grade 1 = Minimal perceptible erythema

Grade 2 = Asymptomatic well defined erythema

Grade 3 = Symptomatic erythema persisting more than 24 hr.

Grade 4 = Severely erythema with edema, blister

**Cause of Phototoxic

TP = Treatment protocol: Dose UVA/UVB too high

PM = Patient variable : Medication ex. MTX, Doxycycline, Diuretic, Coal tar

PD = Patient variable : Concurrent disease

LT = Loss treatment

ES = Excessive expose to sunlight

O = Others

ผู้บันทึก.....

(.....)

วันที่.....

Figure 3.3 Case Record Form (Cont.)

3.3 Data Collection

3.3.1 Inclusion Criteria

3.3.1.1 Male and Female

3.3.1.2 All age ranges

3.3.1.3 Diagnosis of phototoxic reactions due to Phototherapy

3.3.2 Exclusion Criteria

Patients with incomplete treatment records.

3.3.3 Study Location

The study was conducted at the Institute of Dermatology, Bangkok, Thailand.

3.4 Data Analysis

Demographic and descriptive data were expressed as absolute and relative frequencies for categorical variables and as medians and interquartile ranges (IQR) for non-normally distributed quantitative variables. The chi-squared (χ^2) test was used to compare AE incidences between sex, occupation, season, and skin types, the Mann-Whitney U test was used to compare non-normally distributed quantitative variables, the Binary Logistic Regression was used to predict the relationship between multiple factors (dichotomy) , and the Multiple Logistic Regression test to predict the relationship between an individual factor and doses. The magnitude of associations was measured using an odds ratio (OR) with a 95% confidence interval (95% CI). P-values <0.05 were considered statistically significant. All analyses were performed using Excel and IBM SPSS Statistics for Macintosh, Version 23, License No. 1975-01566-C.

Chapter 4

Research Results and Discussion

4.1 Result 1

4.1.1 Patient Demographics and Treatment Overview

From October 2015 through September 2020, 64,629 phototherapy treatment sessions were carried out at the Institute of Dermatology in Thailand. This study specifically analyzed a sample of 200 sessions of phototoxic reaction from 148 patients who had phototoxic reaction during their course of phototherapy. The gender distribution was as follows: 30.5% (n=61) were male, and 69.5% (n=139) were female. The median age of this group was 45.21 years. Importantly, all patients exhibited symptoms of a cutaneous reaction after their last phototherapy session. They met both inclusion and exclusion criteria before starting the research protocol.

Age-wise, 6% (n=12) of the patients were under 20. When examining the Fitzpatrick skin type distribution, a notable majority, 81.5% (n=163), were classified as type IV. The subsequent most common was type III, present in 12.5% (n=25) of the patients, and type V was found in 6% (n=12). Our study contains no patients with Fitzpatrick skin types I, II, or VI.

4.1.2 Clinical Presentation and Phototoxicity

Throughout the research period, 200 sessions of phototoxic reactions represent 0.3% of the overall treatments administered. Regarding the specific dermatoses treated, vitiligo topped the list, accounting for 54% of the cases. Psoriasis vulgaris followed this at 24%, Mycosis fungoides at 13.5%, and Pityriasis alba at 3%. Other conditions such as Pityriasis lichenoides chronica, Atopic dermatitis, Prurigo

nodularis, Pityriasis lichenoides, Actinic Prurigo, Granuloma annulare, and Localized scleroderma each represented 0.5% of the treated cases.

In examining the causative agents for phototoxic responses, Narrowband UVB (NBUVB) was implicated in the majority, responsible for 84% (n=168) of these reactions. This was followed by the 308 nm excimer lamp, accounting for 11% (n=22). The systemic PUVA and topical PUVA were responsible for 2.5% (n=5) and 2.0% (n=4), respectively. UVA1 was the least common cause, responsible for just 0.5% (n=1) of the reactions.

The severity of the phototoxic reactions was categorized into grades. Grade 3 reactions were predominant, making up 74.5% (n=149). This was followed by grades 4, 2, and 1, which represented 12%, 10.5%, and 3%, respectively. A deeper analysis of grade 3 reactions revealed that 86.58% (n=129) were due to NB-UVB, 10.74% resulting from the 308 nm excimer lamps, and 2.68% were attributed to systemic PUVA.

When evaluating the average number of cycles leading to a phototoxic reaction, NB-UVB stood at 38.2 times, systemic PUVA at 33.8 times, topical PUVA at 10 times, UVA1 at 6 times, and the 308 nm excimer lamp at 24.05 times. In terms of the total cumulative dosage, the averages were 42,238.52 mJ/cm^2 for NB-UVB, 220.38 J/cm^2 for systemic PUVA, 19.33 J/cm^2 for topical PUVA, 300 J/cm^2 for UVA1, and 10,352.64 J/cm^2 for the 308 nm excimer lamp.

Seasonal variations also played a role in phototoxic reactions. The rainy season saw the highest incidences, accounting for 43% (n=86) of the cases. Followed by the winter and summer seasons with 30.5% (n=61) and 26.5% (n=53), respectively.

A detailed breakdown of clinical and epidemiological characteristics related to phototoxicity can be found in Table 4.1.

Table 4.1 Clinical and Epidemiological Characteristics According to Phototoxicity

	Total (n=200)	NB-UVB *(n=168)*	Systemic PUVA *(n=5)*	Toical PUVA *(n=4)*	UVA1 *(n=1)*	308 nm Excimer lamp *(n=22)*
Sex, *n (%)*						
Male	61 (30.5)	45 (26.8)	2 (40.0)	4 (100.0)	1 (100.0)	9 (40.9)
Female	139 (69.5)	123 (73.2)	3 (60.0)	0 (0)	0 (0)	13 (59.1)
Age						
Years, mean ± (SD)	45.21 (16.01)	45.4 (14.91)	61 (11.64)	58.75 (5.5)	28	38.45 (21.81)
Skin Type, *n (%)*						
I and II	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
III	25 (12.5)	21 (12.5)	1 (20.0)	0 (0)	0 (0)	3 (13.6)
IV	163 (81.5)	137 (81.5)	4 (80.0)	2 (50.0)	1 (100.0)	19 (86.4)
V	12 (6.0)	10 (6.0)	0 (0)	2 (50.0)	0 (0)	0 (0)
VI	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dermatosis, *n (%)*						
Vitiligo	108 (54.0)	83 (49.4)	0 (0)	4 (100.0)	0 (0)	21 (95.5)
Psoriasis vulgaris	48 (24.0)	47 (28.0)	1 (20.0)	0 (0)	0 (0)	0 (0)
Mycosis fungoides	27 (13.5)	22 (13.1)	4 (80.0)	0 (0)	0 (0)	1 (4.5)
Pityriasis alba	6 (3.0)	6 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)
Pityriasis lichenoides chronica	3 (1.5)	3 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)
Atopic dermatitis	1 (0.5)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Prurigo nodularis	1 (0.5)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Pityriasis lichenoides	1 (0.5)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)

n = number of sessions of phototoxic reaction

Table 4.1 Clinical and Epidemiological Characteristics According to Phototoxicity (Cont.)

	Total (n=200)	NB-UVB *(n=168)*	Systemic PUVA *(n=5)*	Toical PUVA *(n=4)*	UVA1 *(n=1)*	308 nm Excimer lamp *(n=22)*
Actinic Prurigo	1 (0.5)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Granuloma annulare	1 (0.5)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Localized scleroderma	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (100.0)	0 (0)
Other[a]	2 (1.0)	2 (1.2)	0 (0)	0 (0)	0 (0)	0 (0)
Current cycle, mean ± SD	35.8	38.2	33.8	10	6	24.05
Phototoxic Dose, mean ± SD		1379.04 mJ/cm^2	8.78 J/cm^2	2 J/cm^2	50 J/cm^2	722.09 mJ/cm^2
Total Cumulative Dose, mean ± SD		42238.52 mJ/cm^2	220.38 J/cm^2	19.33 J/cm^2	300 J/cm^2	10352.64 mJ/cm^2
Level of Phototoxic, *n (%)*						
Grade 1	6 (3.0)	6 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)
Grade 2	21 (10.5)	18 (10.7)	1 (20.0)	0 (0)	1 (100.0)	1 (4.5)
Grade 3	149 (74.5)	129 (76.8)	4 (80.0)	0 (0)	0 (0)	16 (72.7)
Grade 4	24 (12.0)	15 (8.9)	0 (0)	4 (100.0)	0 (0)	5 (22.7)
Expose time to sunlight, *n (%)*						
Indoor worker	26 (13.0)	14 (8.3)	1 (20.0)	2 (50.0)	0 (0)	9 (40.9)
Outdoor worker	9 (4.5)	9 (5.4)	0 (0)	0 (0)	0 (0)	0 (0)
Seasons, *n (%)*						
Summer (Mid February-Mid May)	53 (26.5)	45 (26.8)	0 (0)	1 (25.0)	0 (0)	7 (31.8)

n = number of sessions of phototoxic reaction

Table 4.1 Clinical and Epidemiological Characteristics According to Phototoxicity (Cont.)

	Total (n=200)	NB-UVB *(n=168)*	Systemic PUVA *(n=5)*	Toical PUVA *(n=4)*	UVA1 *(n=1)*	308 nm Excimer lamp *(n=22)*
Rainy (Mid May-Mid October)	86 (43.0)	69 (41.1)	4 (80.0)	1 (25.0)	1 (100.0)	11 (50.0)
Winter (Mid October-Mid February)	61 (30.5)	54 (32.1)	1 (20.0)	2 (50.0)	0 (0)	4 (18.2)

n = number of sessions of phototoxic reaction

[a]Other skin changes due to chronic exposure to nonionizing radiation. SD: standard deviation.

4.2 Result 2

4.2.1 Etiology of Phototoxic Reactions

Our investigation unveiled that the leading contributors to phototoxicity were the 3 main causes. The first is the patient-related variables in 54.0% (n=108), followed by treatment protocol in 49.5% (n=99) and technical error in 2.5% (n=5). In a variety of patient-related variables that influence phototoxic reactions. Solar radiation appeared as a significant component, with 9% of the cases (n=18) reporting excessive sunlight exposure. The influence of concomitant drugs was also notable, with coal tar, methotrexate, doxycycline, and diuretics resulting in 8.5% (n=17) of phototoxic incidents. A total of 6% (n=12) of the cases failed to adhere to the prescribed treatment regimens, emphasizing the significance of patient compliance in therapeutic outcomes.

Several behavioral and physiological characteristics were also considered, each of which contributed to 2.5% (n=5) of phototoxic reactions. Among these were instances of underwear displacement between consecutive visits, indicating potential noncompliance or misunderstanding of post-phototherapy instructions; inherent skin

thinness, which may predispose to heightened sensitivity to UV exposure; mechanical irritation from lesion rubbing; and the selection of inappropriate protective clothing sizes, emphasizing the importance of patient education on protective measures.

Furthermore, inadequate sunscreen application resulted in 2.0% (n=4) of the reactions, indicating a failure to implement preventive strategies against UV-induced damage, while concurrent diseases represent an equal percentage of the reactions, indicating a multifactorial dimension to patient vulnerability. Despite these findings, a significant proportion of cases, 16.5% (n=33), remained of uncertain etiology, revealing a gap in understanding that requires more study.

Narrowband UVB (NB-UVB) emerged as the predominant modality associated with phototoxic responses across all identified causes of phototoxicity.

A comprehensive categorization of the causes of phototoxicity as per the administered phototherapy modalities is provided in Table 4.2.

Table 4.2 The Causes of Phototoxicity According to Phototherapy

Cause of Phototoxicity	Total *(n=200)* *(%)*	NB-UVB *(n=168)*	Systemic PUVA *(n=5)*	Topical PUVA *(n=4)*	UVA1 *(n=1)*	308 nm excimer lamp *(n=22)*
Treatment protocol[a]	99 (49.5)	85 (50.6)	2 (40.0)	0 (0)	0 (0)	12 (54.5)
Patient variable:	108 (54.0)	90 (53.6)	3 (60.0)	3 (75.0)	1 (100.0)	11 (50.0)
Medication[b]	17 (8.5)	14 (8.3)	2 (40.0)	1 (25.0)	0 (0)	0 (0)
Concurrent diseases	4 (2.0)	4 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)
Loss Treatment	12 (6.0)	12 (7.1)	0 (0)	0 (0)	0 (0)	0 (0)
Excessive exposure to sunlight	18 (9.0)	15 (8.9)	0 (0)	0 (0)	0 (0)	3 (13.6)
Displacement of underwear from the previous visit	5 (2.5)	5 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 4.2 The Causes of Phototoxicity According to Phototherapy (Cont.)

Cause of Phototoxicity	Total *(n=200)* *(%)*	NB-UVB *(n=168)*	Systemic PUVA *(n=5)*	Topical PUVA *(n=4)*	UVA1 *(n=1)*	308 nm excimer lamp *(n=22)*
Rubbing the lesion	5 (2.5)	4 (2.4)	0 (0)	0 (0)	0 (0)	1 (4.5)
Wearing various protection sizes	5 (2.5)	5 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)
Not apply sunscreen	4 (2.0)	4 (2.4)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown cause	33 (16.5)	25 (14.9)	0 (0)	2 (50.0)	1 (100.0)	5 (22.7)
Technical error[c]	5 (2.5)	4 (2.4)	0 (0)	1 (25.0)	0 (0)	0 (0)

n = number of sessions of phototoxic reaction.

[a]Treatment protocol: Dose UVA/UVB too high. [b]Patient variable: Medication ex. Methotrexate, Doxycycline, Diuretic, Coal tar. [c]Technical Error - Incorrect dose/ addition of UVB Instead of UVA radiation.

4.3 Result 3

4.3.1 Phototoxicity Across Gender, Age, and Skin Types

Upon analyzing the 200 phototherapy sessions in the study, it was found that grade 3 phototoxicity was markedly more prevalent among females, with 55% (n=110) affected compared to 19.5% (n=39) of males. Age-wise, all phototoxicity grades prominently clustered within the 40 to 50 year old age bracket.

Skin type plays a significant role in phototoxicity predisposition. Those with Fitzpatrick skin type IV, representing 81.5% (n=163) of the phototherapy sessions, were highly susceptible to phototoxic reactions. Specifically, grade 3 reactions were dominant at 61.5% (n=123), trailed by grade 4 at 10% (n=20), grade 2 at 7% (n=14), and grade 1 at 3% (n=6). Additionally, 12.5% (n=25) of the patients were Fitzpatrick skin type III, and 6% (n=12) were type VI.

Regarding specific dermatological conditions, vitiligo patients were notably affected by phototoxic reactions. In 41.5% (n=83) of these patients, grade 3 phototoxicity was the predominant observation, followed by grade 4 in 10.5% (n=21). Among patients diagnosed with Psoriasis vulgaris, 17% (n=34) exhibited grade 3 phototoxic reactions, with grade 2 seen in 4% (n=8). For Mycosis fungoides patients, grade 3 phototoxic reactions manifested in 10.5% (n=21) cases, whereas grade 2 was observed in 3% (n=6).

4.3.2 Statistical Analysis and Seasonal Variations

Several factors showed a statistically significant association with phototoxicity levels. The diagnosis (p=0.002), presence of concurrent diseases (p=0.002), excessive exposure to sunlight (p=0.029), and thin skin (p<0.001) all demonstrated significant correlations with the severity of phototoxic reactions. Seasonal patterns also emerged; the summer season was statistically significant concerning the severity of phototoxic reactions, especially in the higher grades 3 and 4 (p=0.046). A detailed depiction of patients' characteristics, considering the severity of their phototoxic reactions, is provided in Table 4.3.

Table 4.3 Clinical and Epidemiological Characteristics According to the Level of Phototoxicity

Variables	Level of phototoxicity				p-value
	Grade 1 *(n=6)*	Grade 2 *(n=21)*	Grade 3 *(n=149)*	Grade 4 *(n=24)*	
Sex, *n (%)*					NS
Male	2 (33.3)	9 (42.9)	39 (26.2)	11 (45.8)	
Female	4 (66.7)	12 (57.1)	110 (73.8)	13 (54.2)	
Age					NS
Years, mean ± (SD)	48.83 (11.55)	43.52 (14.01)	45.4 (16.34)	44.54 (17.12)	
Skin Type, *n (%)*					NS
I and II	0 (0)	0 (0)	0 (0)	0 (0)	N/A
III	0 (0)	5 (23.8)	18 (12.1)	2 (8.3)	NS

Table 4.3 Clinical and Epidemiological Characteristics According to the Level of Phototoxicity (Cont.)

Variables	Level of phototoxicity				
	Grade 1 *(n=6)*	Grade 2 *(n=21)*	Grade 3 *(n=149)*	Grade 4 *(n=24)*	p-value
IV	6 (100.0)	14 (66.7)	123 (82.6)	20 (83.3)	NS
V	0 (0)	2 (9.5)	8 (5.4)	2 (8.3)	NS
VI	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Dermatosis, *n (%)*					0.002
Vitiligo	1 (16.7)	3 (14.3)	83 (55.7)	21 (87.5)	
Psoriasis vulgaris	3 (50.0)	8 (38.1)	34 (22.8)	3 (12.5)	
Mycosis fungoides	0 (0)	6 (28.6)	21 (14.1)	0 (0)	
Pityriasis alba	2 (33.3)	2 (9.5)	2 (1.3)	0 (0)	
PLC	0 (0)	1 (4.8)	2 (1.3)	0 (0)	
Atopic dermatitis	0 (0)	0 (0)	1 (0.7)	0 (0)	
Prurigo nodularis	0 (0)	0 (0)	1 (0.7)	0 (0)	
PLEVA	0 (0)	0 (0)	1 (0.7)	0 (0)	
Actinic Prurigo	0 (0)	0 (0)	1 (0.7)	0 (0)	
Granuloma annulare	0 (0)	0 (0)	1 (0.7)	0 (0)	
Localized scleroderma	0 (0)	1 (4.8)	0 (0)	0 (0)	
Other[a]	0 (0)	0 (0)	2 (1.3)	0 (0)	
Cause of Phototoxicity, *n (%)*					
Treatment protocol[b]	4 (66.7)	8 (38.1)	80 (53.7)	7 (29.2)	NS
Patient variables:					
Medication[c]	0 (0.0)	0 (0.0)	15 (10.1)	2 (8.3)	NS
Concurrent disease	1 (16.7)	2 (9.5)	1 (0.7)	0 (0.0)	0.002
Loss Treatment	0 (0.0)	3 (14.3)	8 (5.4)	1 (4.2)	NS
Excessive exposure to sunlight	0 (0.0)	1 (4.8)	11 (7.4)	6 (25.0)	0.029
Displacement of underwear from the previous visit	0 (0.0)	1 (4.8)	4 (2.7)	0 (0.0)	NS
Thin skin	0 (0.0)	2 (9.5)	0 (0.0)	3 (12.5)	<0.001
Rubbing the lesion	0 (0.0)	1 (4.8)	4 (2.7)	0 (0.0)	NS

Table 4.3 Clinical and Epidemiological Characteristics According to the Level of Phototoxicity (Cont.)

Variables	Level of phototoxicity				p-value
	Grade 1 *(n=6)*	Grade 2 *(n=21)*	Grade 3 *(n=149)*	Grade 4 *(n=24)*	
Wearing various protectic sizes	0 (0.0)	0 (0.0)	5 (3.4)	0 (0.0)	NS
Not apply sunscreen	0 (0.0)	1 (4.8)	2 (1.3)	1 (4.2)	NS
Unknown cause	1 (16.7)	2 (9.5)	25 (16.8)	5 (20.8)	NS
Technical error[d]	0 (0.0)	1 (4.8)	2 (1.3)	2 (8.3)	NS
Seasons, n (%)					NS
Summer	1 (16.7)	2 (9.5)	39 (26.2)	11 (45.8)	0.046
Rainy	2 (33.3)	12 (57.1)	64 (43.0)	8 (33.3)	NS
Winter	3 (50.0)	7 (33.3)	46 (30.9)	5 (20.8)	NS

n = number of sessions of phototoxic reaction

[a]Other skin changes due to chronic exposure to nonionizing radiation. PLC: Pityriasis lichenoides chronica. PLEVA: Pityriasis lichenoides et varioliformis acuta. [b]Treatment protocol: Dose UVA/UVB too high. [c]Patient variables: Medication ex. Methotrexate, Doxycycline, Diuretic, Coal tar. [d]Technical Error - Incorrect dose/ addition of UVB Instead of UVA radiation. SD: standard deviation. NS: not significant.

4.4 Discussion

Phototherapy has emerged as a crucial tool in managing various dermatological diseases. However, its efficacy is influenced by many factors, which, when not appropriately managed, can lead to adverse effects. A spectrum of variables, ranging from the equipment used, the proficiency and expertise of the healthcare staff, to the methods employed during the treatment process, all play significant roles in determining the therapeutic outcome and the potential risk for adverse effects.

Despite the ubiquity of phototherapy in dermatological treatments, it is notable that there is a shortage of comprehensive guidelines or protocols addressing the management of its associated adverse effects. This gap in the literature and clinical

guidelines underscores the need for studies that delve into the complications and challenges faced during phototherapy, particularly phototoxic reactions.

Moreover, regional variations can influence the prevalence and presentation of these adverse effects. Thailand poses unique challenges with its distinct climatic conditions characterized by prolonged sun exposure. Extended sun exposure can potentiate the effects of phototherapy, leading to heightened risks of phototoxic reactions. Yet, surprisingly, there has been no documented report addressing the prevalence of these phototoxic reactions in the context of the Thai population undergoing phototherapy.

This current research, therefore, represents a pioneering effort in this domain. This study fills a critical gap by focusing on the prevalence of phototoxic reactions related to phototherapy, especially with the total number of treatment sessions in a phototherapy unit. It provides invaluable insights into the challenges and implications of administering phototherapy in environments with extended sun exposure. It paves the way for future studies and potential development of region-specific guidelines.

The incidence of adverse events associated with Phototherapy in clinical settings has been extensively reported to range from 0.8% to 94%. Martin *et al*. (2007) reported that the total number of acute adverse events recorded for all phototherapy treatments was 0.8% (70 of 8784 treatments). The report by Belinchon et al. (2020) noted the rate of AEs with Phototherapy was 19.1%. Vazquez et al. (2018) reported that Phototoxic reactions are more frequent in patients with light skin phototypes (I and II). Previously published AE rates for NB-UVB ranged from 10% to 94% (Ibbotson et al., 2004; Green et al., 1988; Coven et al., 1997; Gordon et al., 1999; Green et al., 1992). Phototoxicity due to PUVA in 10.9% of patients. Problems with the treatment protocols were the primary cause reported (Morison, Marwaha, and Beck, 1997).

According to this study's findings, NB-UVB phototherapy accounted for 84% of treatments, which aligns with current therapeutic recommendations and several

regional, national, and worldwide publications. Vitiligo is the most common dermatosis treated by our phototherapy unit. Phototherapy is a mainstay in vitiligo treatment, with extensive evidence-based results and valuable experience for this dermatosis (Ibbotson et al., 2004; Bae et al., 2017). Our results showed that the rate of acute adverse events encountered over five years in a working phototherapy unit was low (200 out of 64,629 treatments, 0.3%), and only 24 were considered phototoxic reactions grade 4 (0.04% of all treatments). There was no difference in the proportion of men and women who experienced adverse effects and no significant differences across skin phototypes. Patients with adverse events were slightly older.

The rate of acute adverse events in this study was low, at 0.3%, although around half of these were caused by the treatment protocol (UVA/UVB doses too high). Hence, when increasing the dose, the patient should be informed of the possibility of a phototoxic reaction; once the phototoxic reaction improves, there is no need to increase the dose.

This research presents the 200 sessions of phototoxic reaction from phototherapy in a cohort of 148 patients in a 5 year-study period. It is important to note that an individual patient may has unexpected phototoxic reactions in their course of phototherapy. There are three possible causes for these reactions. The first, regarding the treatment protocol ordered by dermatologist, patients may have a risk of phototoxic reactions due to increasing UVA/UVB dosage in each phototherapy sessions as a standard phototherapy protocol. The second category, known as patient-related variables, comprises a variety of variables. It includes medication-induced photosensitivity caused by agents like methotrexate and doxycycline, concurrent medical conditions, non-compliance with treatment regimens, excessive sunlight exposure, misplacement of protective clothing, sensitive skin areas such as the neck and inner limbs, friction-induced injury to the affected region, and insufficient protective measures including inadequate use of sunscreen products. However, if the patient is unable to clarify the cause, we may needs to categorized as unknown etiology from patient-related variables. The last category comprises

technical errors, such as the unintentional replacement of UVA radiation with UVB radiation or the incorrect administration of dosages.

The elderly were associated with an increased likelihood of phototoxic reactions and higher levels of phototoxicity. Current medications (such as methotrexate, doxycycline, diuretics, and coal tar), exposure to sunlight following treatment, and patients with thin skin are causes of phototoxicity compared to the phototherapy modality. The summertime and concurrent disease (Allergic rhinitis, Supraventricular tachycardia, Thalassemia, Chronic HBV, Fatty liver) were statistically significant concerning the level of phototoxicity. Hence, providing additional information to patients with these risk factors for AEs and enhancing monitoring and control in these groups could assist in the prevention and rapid treatment of AEs, thereby facilitating the completion of the treatment regimen. However, the data included in this study were collected through a clinical audit rather than through traditional research. Therefore, they may be limited by the pressures and errors that can occur in a clinical setting practice. In addition, a percentage of patients receiving therapy during this period will have previously experienced well-tolerated treatment sessions, which may have contributed to the low incidence of adverse events.

Also, it is noted that the adverse event data presented in this study are particular to dose schedules based on pretreatment MED (minimal erythema dose) or MPD (minimal phototoxic dose) testing for each patient. Nevertheless, not all phototherapy units in Thailand follow this regimen. Consequently, the incidence of acute adverse effects, particularly erythema, may vary. Mainly, specific dosage regimens rely on the induction of an erythemal response to calculate dosage increments during the initial phases. This audit's low rate of adverse events demonstrates the advantages of following this regimen.

This study does have some limitations. First, the study is a single-center retrospective investigation carried out in areas with prolonged sun exposure, which may limit the generalization of the results. Second, the rareness of some dermatoses

may determine findings on dermatoses-related adverse events. Third, the absence of some skin phototypes may prevent judgments regarding dermatosis-related adverse effects. And fourth, several patients discontinued therapy for unspecified reasons, which might indicate an underestimation of the incidence of adverse events (AEs).

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

The retrospective study at the Institute of Dermatology, Thailand, unveiled the prevalence of phototoxic reactions attributable to Phototherapy in Thai patients. The data denotes a surprisingly low prevalence rate, at just 0.3%, of such reactions linked to Phototherapy. The most recurrent phototoxic reaction was associated with the skin condition Vitiligo. Looking deeper into demographics, female patients, those with skin type IV, undergoing NB-UVB treatment, and those diagnosed with vitiligo, showcased a high prevalence to phototoxic reactions. Within the spectrum of severity, grade 3 phototoxic reactions were the most commonly encountered. The primary cause of these reactions was a combination of patient variables and technical errors. These factors included patients' medications, prevailing health conditions, missed treatments, excessive sunlight exposure, unusual instances like shifts in underwear placement from the previous session, and other technical oversights. Subsequently, administering overly high doses of UVA/UVB during treatment was pinpointed as the next significant contributing factor.

Many external and internal factors, ranging from age, existing health conditions, medications being taken, and excessive sun exposure, play pivotal roles in instigating phototoxic reactions. Additionally, our data highlights the summer season as an exacerbating element, intensifying symptomatic phototoxic reactions, especially those within the grade 3 and 4 brackets. All these variables collectively form a matrix of risk factors predisposing patients to phototoxic reactions during Phototherapy.

5.2 Recommendations

Phototherapy is a formidable and safe intervention for managing persistent dermatological conditions spanning long durations. While its safety profile is commendable, safeguarding patient well-being remains of utmost priority. Understanding the spectrum of risk factors and their possible consequences, it is essential to implement specific preventive measures and management strategies. Primarily, clinicians must ensure that patients are well-informed about the potentiality of a phototoxic reaction. A cautious and calculated approach is imperative if a dose escalation is necessary. Enhanced monitoring mechanisms should be instituted, especially for those with multiple risk factors. Moreover, comprehensive patient counseling sessions, both before and after the conclusion of phototherapy, are instrumental in setting realistic expectations and preemptively addressing potential concerns.

References

Almutawa, F., Alnomair, N., Wang, Y., Hamzavi, I., & Lim, H. W. (2013). Systematic review of UV-based therapy for psoriasis. *American journal of clinical dermatology*, *14*(2), 87–109. doi: 10.1007/s40257-013-0015-y

Armstrong, A. W., & Read, C. (2020). Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA*, *323*(19), 1945–1960. doi: 10.1001/jama.2020.4006

Bae, J. M., Jung, H. M., Hong, B. Y., Lee, J. H., Choi, W. J., Lee, J. H., & Kim, G. M. (2017). Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. *JAMA dermatology*, *153*(7), 666–674. doi: 10.1001/jamadermatol.2017.0002

Belinchón, I., Sánchez-Pujol, M. J., Docampo, A., Cuesta, L., Schneller-Pavelescu, L., & Ramos-Rincón, J. M. (2020). Adverse Events Leading to Discontinuation of Phototherapy: An Observational Study. *Acta dermato-venereologica*, *100*(6), adv00089. doi: 10.2340/00015555-3453

Chen, X., Yang, M., Cheng, Y., Liu, G. J., & Zhang, M. (2013). Narrowband ultraviolet B phototherapy versus broadband ultraviolet B or psoralen-ultraviolet A photochemotherapy for psoriasis. *The Cochrane database of systematic reviews*, (10), CD009481. doi: 10.1002/14651858.CD009481.pub2

Costin, G. E., & Hearing, V. J. (2007). Human skin pigmentation: melanocytes modulate skin color in response to stress. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*, *21*(4), 976–994. doi.org/10.1096/fj.06-6649rev

Coven, T. R., Burack, L. H., Gilleaudeau, R., Keogh, M., Ozawa, M., & Krueger, J. G. (1997). Narrowband UV-B produces superior clinical and histopathological resolution of moderate-to-severe psoriasis in patients compared with broadband UV-B. *Archives of dermatology*, *133*(12), 1514–1522.

Di Bartolomeo, L., Irrera, N., Campo, G. M., Borgia, F., Motolese, A., Vaccaro, F., … Vaccaro, M. (2022). Drug-Induced Photosensitivity: Clinical Types of Phototoxicity and Photoallergy and Pathogenetic Mechanisms. *Frontiers in allergy*, *3*, 876695.

References (Cont.)

Elmets, C. A., Lim, H. W., Stoff, B., Connor, C., Cordoro, K. M., Lebwohl, M., … Menter, A. (2019). Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with Phototherapy. *Journal of the American Academy of Dermatology*, *81*(3), 775–804. doi: 10.1016/j.jaad.2019.04.042

Esmat, S., Hegazy, R. A., Shalaby, S., Hu, S. C., & Lan, C. E. (2017). Phototherapy and Combination Therapies for Vitiligo. *Dermatologic clinics*, *35*(2), 171–192. doi: 10.1016/j.det.2016.11.008

Gordon, P. M., Diffey, B. L., Matthews, J. N., & Farr, P. M. (1999). A randomized comparison of narrowband TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *Journal of the American Academy of Dermatology*, *41*(5 Pt 1), 728–732. doi: 10.1016/s0190-9622(99)70008-3

Gouveia, M., Gameiro, A., Coutinho, I., & Gonçalo, M. (2016). Drug-Induced Photosensitivity. *Journal of the Portuguese Society of Dermatology and Venereology*, *74*(2), 123-135. https://doi.org/10.29021/spdv.74.2.548

Green, C., Ferguson, J., Lakshmipathi, T., & Johnson, B. E. (1988). 311 nm UVB phototherapy--an effective treatment for psoriasis. *The British journal of dermatology*, *119*(6), 691–696. doi: 10.1111/j.1365-2133.1988.tb03489.x

Green, C., Lakshmipathi, T., Johnson, B. E., & Ferguson, J. (1992). A comparison of the efficacy and relapse rates of narrowband UVB (TL-01) monotherapy vs. etretinate (re-TL-01) vs. etretinate-PUVA (re-PUVA) in the treatment of psoriasis patients. *The British journal of dermatology*, *127*(1), 5–9. doi: 10.1111/j.1365-2133.1992.tb14815.x

Henry W. Lim. (2019). Phototoxicity and Photoallergy. *Fitzpatrick's dermatology* (9th ed). New York: Mcgraw Hill.

High, W. A., Tomasini, C. F., Argenziano, G., & Zalaudek, I. (2018). Basic principles of dermatology. In J. L. Bolognia, J. V. Schaffer, & L. Cerroni (Eds.), *Dermatology* (4th ed., pp. 1-43). China: Elsevier.

References (Cont.)

Hong, S. B., Park, H. H., & Lee, M. H. (2005). Short-term effects of 308-nm xenon-chloride excimer laser and narrowband ultraviolet B in the treatment of vitiligo: a comparative study. *Journal of Korean medical science*, *20*(2), 273–278. doi: 10.3346/jkms.2005.20.2.273

Honigsmann, H., & Schwarz, T. (2018). Ultraviolet Therapy. In J. L. Bolognia, J. V. Schaffer, & L. Cerroni (Eds.), *Dermatology* (4th ed., pp. 2325-40). China: Elsevier.

Ibbotson, S. & Dawe, R. (2016). Cutaneous Photosensitivity Diseases. In C. E. M. Graffiths, J. Barker, T. Bleiker, R. Chalmers & D. Creamer (Eds.), *Rook's Textbook of Dermatology* (9th ed., pp. 127.1-36). United Kingdom: Blackwell Publishing.

Ibbotson S., (2018). Drug and chemical induced photosensitivity from a clinical perspective. *Photochemical & photobiological sciences : Official journal of the European Photochemistry Association and the European Society for Photobiology*, *17*(12), 1885–1903. doi: 10.1039/c8pp00011e

Ibbotson, S. H., Bilsland, D., Cox, N. H., Dawe, R. S., Diffey, B., Edwards, C., … British Association of Dermatologists (2004). An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. *The British journal of dermatology*, *151*(2), 283–297. doi: 10.1111/j.1365-2133.2004.06128.x

Kemény, L., Varga, E., & Novak, Z. (2019). Advances in Phototherapy for psoriasis and atopic dermatitis. *Expert review of clinical immunology*, *15*(11), 1205–1214. doi: 10.1080/1744666X.2020.1672537

Kim, W. B., Shelley, A. J., Novice, K., Joo, J., Lim, H. W., & Glassman, S. J. (2018). Drug-induced phototoxicity: A systematic review. *Journal of the American Academy of Dermatology*, *79*(6), 1069–1075. doi.org/10.1016/j.jaad.2018.06.061

References (Cont.)

Martin, J. A., Laube, S., Edwards, C., Gambles, B., & Anstey, A. V. (2007). Rate of acute adverse events for narrowband UVB and Psoralen-UVA phototherapy. *Photodermatology, photoimmunology & photomedicine*, *23*(2-3), 68–72. doi: 10.1111/j.1600-0781.2007.00278.x

Matos, T. R., Ling, T. C., & Sheth, V. (2016). Ultraviolet B radiation therapy for psoriasis: Pursuing the optimal regime. *Clinics in dermatology*, *34*(5), 587–593. doi: 10.1016/j.clindermatol.2016.05.008

Morison, W. L., Marwaha, S., & Beck, L. (1997). PUVA-induced phototoxicity: incidence and causes. *Journal of the American Academy of Dermatology*, *36*(2 Pt 1), 183–185. doi: 10.1016/s0190-9622(97)70277-9

Ortiz-Salvador, J. M., & Pérez-Ferriols, A. (2017). Phototherapy in Atopic Dermatitis. *Advances in experimental medicine and biology*, *996*, 279–286. doi: 10.1007/978-3-319-56017-5_23

Pereira, A. S., Xará, J., & Gonçalo, M. (2022). Drug-induced photosensitivity. *Portuguese Journal of Dermatology and Venereology*, *80*(2), 104-117. doi: 10.24875/PJDV.M22000027

Rodenbeck, D. L., Silverberg, J. I., & Silverberg, N. B. (2016). Phototherapy for atopic dermatitis. *Clinics in dermatology*, *34*(5), 607–613. doi: 10.1016/j.clindermatol.2016.05.011

Singer, S., & Berneburg, M. (2018). Phototherapy. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG*, *16*(9), 1120–1129. doi: 10.1111/ddg.13646

Stern, R. S., & PUVA Follow-Up Study (2012). The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *Journal of the American Academy of Dermatology*, *66*(4), 553–562. doi: 10.1016/j.jaad.2011.04.004

Thu, H. D. T., Hong, N. D. T., Van, T. N., Minh, P. P. T., Van, T. H., Huu, N. D., … Lotti, T. (2019). The Decline of PUVA Therapy in Vietnam: Effective Treatment of Narrow Band UVB in Vietnamese Vitiligo Patients. *Open access Macedonian journal of medical sciences*, *7*(2), 256–258.

References (Cont.)

Van, T. N., Van, T. H., Minh, P. P. T., Trong, H. N., Van, T. C., Huu, N. D., … Lotti, T. (2019). Efficacy of Narrow - Band UVB Phototherapy versus PUVA Chemophototherapy for Psoriasis in Vietnamese Patients. *Open access Macedonian journal of medical sciences*, *7*(2), 227–230. doi: 10.3889/oamjms.2019.057

Vázquez-Osorio, I., González-Delgado, S., Suárez-García, C., Gonzalvo-Rodríguez, P., & Rodríguez-Díaz, E. (2018). Blisters Induced by PUVA: A Report of 5 Cases. Ampollas inducidas por PUVA. Presentación de 5 casos. *Actas dermo-sifiliograficas*, *109*(8), e11–e16. doi: 10.1016/j.ad.2017.10.011

Ware, O. R., Guiyab, J., & Okoye, G. A. (2020). Phototherapy in Skin of Color. *Dermatologic clinics*, *38*(1), 63–69. doi.org/10.1016/j.det.2019.08.006

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