PREVALENCE AND PREDICTION OF DRUG-INDUCED PHOTOSENSITIVITY

A thesis submitted to the University of Manchester for the degree of Doctor of Medicine in the Faculty of Biology, Medicine and Health

2020

Amirah Alrashidi

School of Biological Sciences

Division of Musculoskeletal & Dermatological Sciences

Table of contents

Word count: 42,158

List of tables

List of figures

List of abbreviations

1,25D	1,25-dihydroxy vitamin D
25-OHD	25-hydroxy vitamin D
A&E	Accident and emergency
ACE	Angiotensin-converting enzyme inhibitors
AIP	Acute intermittent porphyria
ANA	Anti-nuclear antibodies
AP	Actinic prurigo
AP-1	Activator protein-1
ARBs	Angiotensin receptor blocker
B cells	B-lymphocytes
BB	Beta-blocker
BB-UVA	Broadband UVA
BCC	Basal cell carcinoma
CAD	Chronic actinic dermatitis
CCBs	Calcium channel blockers
CHS	Contact hypersensitivity
CIE	Commission Internationale de l'Eclairage
DIP	Drug-induced photosensitivity
DLE	Discoid lupus erythematosus
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EBV	Epstein-Barr virus
EPP	Erythropoietic protoporphyria
HCP	Hereditary coproporphyria
HLA	Human leukocyte antigen
HV	Hydroa vacciniforme
ICDRG	International Contact Dermatitis Research Group
IFN-γ	Interferon Gamma
IgE	Immunoglobulin E
IL	Interleukin

IPD	Immediate pigment darkening
LE	Lupus erythematosus
MD	Doctor of Medicine
MED	Minimal Erythema Dose
MHC	Major histocompatibility complex
MM	Malignant melanoma
NB-UVB	Narrowband UVB
NFk-B	Nuclear factor kappa Beta
NSAIDs	Non-steroidal anti-inflammatory drug
PCT	Porphyria cutanea tarda
PDT	Photodynamic therapy
PGE2	Prostaglandin E2
PIDEs	Photo-induced drug eruptions
PLE	Polymorphic light eruption
PPD	Persistent pigment darkening
PPI	Proton pump inhibitor
PT	Photopatch testing
PUVA	Psoralens and UVA photochemotherapy
QIMR	Queensland Institute of Medical Research
RC	Rechallenge test
ROS	Reactive oxygen species
SCC	Squamous cell carcinoma
SCLE	Subacute cutaneous lupus erythematosus
SED	Standard erythema dose
SNRI	Serotonin-norepinephrine reuptake inhibitor
SPF	Sun Protection Factor
SSR	Solar simulated radiation
SSRI	Selective serotonin reuptake inhibitor
SU	Solar urticaria
T cell	T-lymphocyte
TCA	Tricyclic antidepressant
Th1	T-helper cell type1
Th2	T-helper cell type 2
TKI	Tyrosine kinase inhibitor

TNF	Tumour necrosis factor
UPF	Ultraviolet Protection Factor
UVR	Ultraviolet radiation
VP	Variegate porphyria
XP	Xeroderma pigmentosum

Abstract

Background: The prevalence of drug-induced photosensitivity (DIP), and the clinical and photobiological profile of affected patients, is poorly understood. There is limited information on the extent or prevalence of DIP in the UK. Determining which drugs may induce DIP and whether certain patients are more susceptible, would be a significant step in patient management.

Aims: To determine the prevalence of DIP both within photosensitive patients diagnosed in the Photobiology Unit (Salford Royal NHS Foundation Trust) between 2000 and 2016 and the wider community at outpatients' clinics (Salford Royal NHS Foundation Trust). Further, to characterise the clinical and photobiological features of DIP patients and identifying the key culprit drugs.

Methods: Study one: a retrospective review of patients who received a diagnosis of DIP in the Photobiology Unit. Clinical history, phototest results and impact on the quality of life (QoL) associated with DIP were collated. Study two: A questionnaire-based study at Salford Royal outpatients' clinics was undertaken. Information on medicine usage and the effects of sun exposure was collected. Respondents taking potential photosensitising medication and describing a temporally associated atypical sun exposure-response were identified as cases of probable DIP.

Results: The prevalence of DIP for all patients attending the photobiology unit was 5.4% (122 of 2,243). Key culprit drugs were quinine (11.5%), diuretics (10.7%), antifungals (9.8%), and proton pump inhibitors (9.8%). Quality of life (QoL) index over the past week (and year) was classified as moderately impaired in 24% (41% year), very largely impaired in 22% (31% year) and extremely largely impaired in 3.7% (17.2% year). Of the 986 individuals approached in study two, 531 (53.8%) agreed to participate of whom 89.4% (475) were taking 1416 medications, 50.4% being potential photosensitisers. Sun responses were reported by 112 participants, of which a temporal association with the commencement of a potentially photosensitising drug(s) could be identified in ten individuals (2.1%). These ten cases of probable DIP were taking 15 different potential photosensitisers including: statins (6), proton pump inhibitor, omeprazole (5), anti-hypertensives (4) and anti-depressants (4); however, when normalised to the number of participants taking the drug, azathioprine (66.7%), quinine (33.3%) indapamide (25%) and diltiazem (20%) were the drugs most commonly associated with probable DIP. Due to the low numbers of probable DIP identified, further characterisation of participants at risk of DIP was not possible.

Conclusion: The prevalence of DIP and its impact on patients' QoL highlighted the importance of this adverse drug reaction and the need to establish effective strategies for diagnosing and providing appropriate management. Key photosensitisers were identified, including the developing issue of DIP reactions to PPI's. Phototesting, particularly broadband UVA provocation testing, was recognised as an essential diagnostic tool. The questionnaire has the potential to quickly screen for potential cases of DIP, having identified ten probable cases. However, standard phototesting would be required to make a confirmed diagnosis and validate the questionnaire findings.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

COPYRIGHT STATEMENT

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and s/he has given The University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made only in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=2442 0), in any relevant Thesis restriction declarations deposited in the University Library, The University Library's regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in The University's policy on Presentation of Theses

Dedication

To my sister Shereen, for the strength and determination, she provides during my MD journey and to my three children Farah, Bader and Ahmad for their understanding, compassion, love and support. Finally, to Ms Bushra, who is working at the Kuwait Institute for Medical Specializations (KIMS) for her support and encouragement during my study in the UK.

Acknowledgement

I would like to take this opportunity to extend my deepest gratitude to my supervisor, Professor Rachel Watson, for her support, encouragement, and expertise. Despite my MD journey proving to challenge at times, her guidance and feedback have been strong motivational factors in ensuring the successful completion of this work. Similarly, profound gratitude goes to Ms Ann Haylett, a retired nurse, who was working at the Photobiology Unit at Salford Royal Hospital, for her advice and expertise.

I am also most grateful to the Ministry of Health, Kuwait, and the Kuwait Institute for Medical Specializations (KIMS) for funding this project and giving me the opportunity to study at the University of Manchester.

Special thanks to Joanne Osman a Clinical Research Nurse at Photobiology Unit at Salford Royal Hospital, for her help and support with ethics application. Similarly, profound gratitude goes to Dr Elizabeth Marjanovic statistician working at the Division of Musculoskeletal & Dermatological Sciences, University of Manchester, for her advice and expertise during second project data collection and analysis. Also, I would like to thank Dr.Ahad Tashmeeta for her contribution. I would also thank Professor Lesley Rhodes, professor of experimental dermatology at the University of Manchester and Professor Adele Green, professor of epidemiology at the QIMR Berghofer Medical Research Institute Brisbane, Australia and Dr Mark Farrar Lecturer in Photobiology; Division of Musculoskeletal & Dermatological Sciences, University of Manchester, for their advice, expertise and contribution.

Publication arising from this thesis

I. Manuscript

Alrashidi, A., Rhodes, L.E., Sharif, J.C., Kreeshan, F.C., Farrar, M.D. and Ahad, T., 2020. Systemic drug photosensitivity—Culprits, impact and investigation in 122 patients. *Photodermatology, Photoimmunology & Photomedicine*, *36*(6), pp.441-451.

II. Abstract

Ahad, T., Haylett, A., Alrashidi, A. and Rhodes, L., 2018. Drug photosensitivity today—Culprits, impact, and investigation: 6887. Journal of the American Academy of Dermatology, 79(3).

Chapter 1: Introduction and literature review

1.1 What is photobiology?

Photobiology is the term used to describe the influence of non-ionising radiation (ultraviolet radiation [UVR], visible light, and infrared radiation) on living organisms, whilst cutaneous photobiology is the study of non-ionising radiation and its interaction with the skin (Diffey and Kochevar, 2007, Hawk et al., 2010, Epstein, 1971).

1.2 Electromagnetic spectrum

The term ‘electromagnetic spectrum’ was first coined by J.C. Maxwell in a series of publications describing the electric and magnetic properties of the electron magnetic spectrum (Maxwell, 1861). The electromagnetic spectrum is a term assigned to the transformation of energy into waves and particles. It consists of different wavelengths, including UVR, microwaves, radio waves, X-rays, and gamma rays (Figure 1 1). The region of interest in photobiology covers the UVR, visible, and infrared regions, collectively known as optical radiation (de l’Eclairage, 1970, Diffey and Kochevar, 2007).

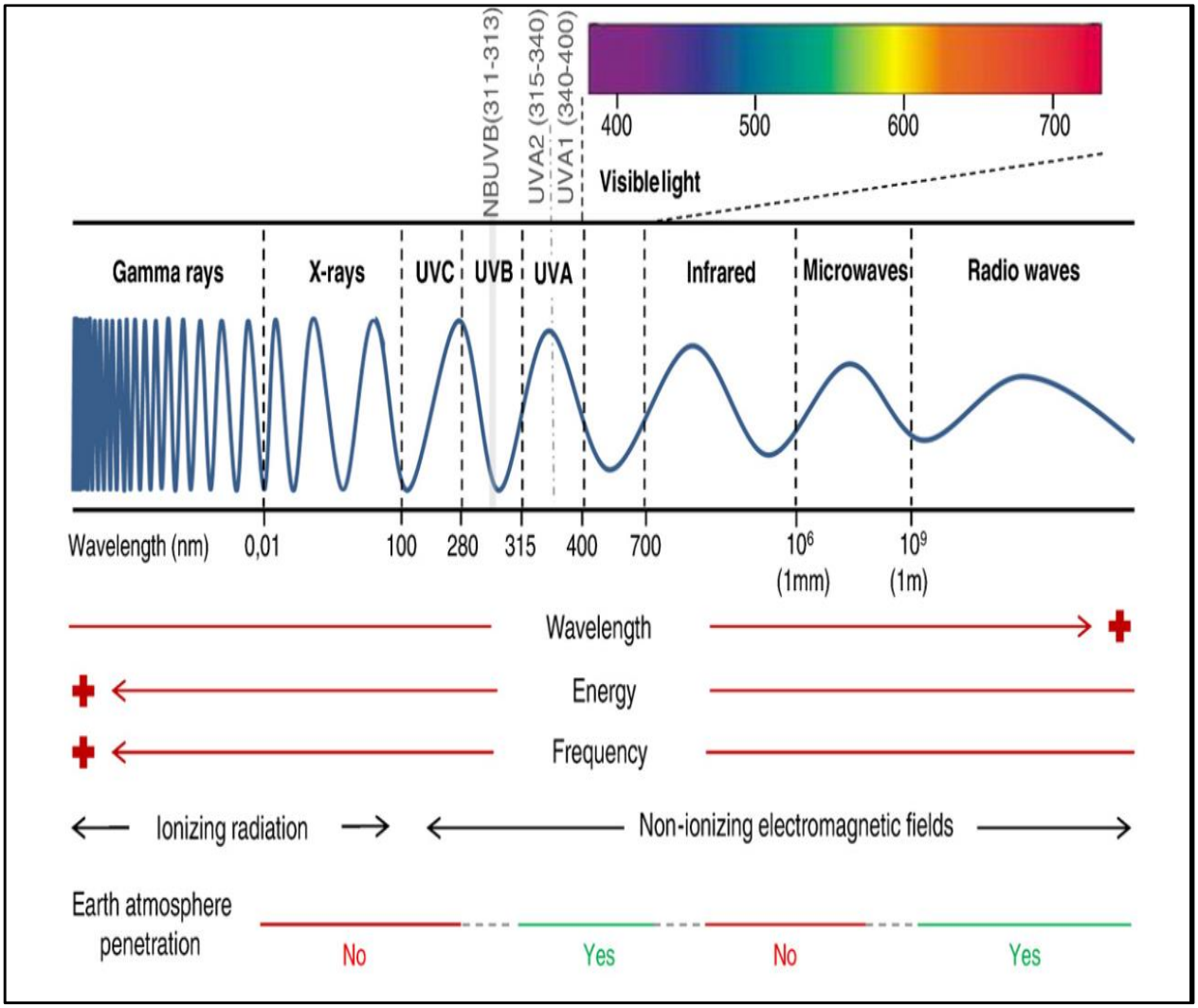


Figure 1-1 The electromagnetic spectrum consists of different wavelengths, including UVR, microwaves, radio waves, X-rays, and gamma rays.

Adapted from (Matos and Sheth, 2016)

1.2.1 Ultraviolet radiation regions

Optical radiation is divided into the following: 50% visible light (which can be recognised by the human eye), 40% infrared, and 10% UVR. Notably, UVR is the most biologically active component of optical radiation, having the most profound effect in terms of diseases and overall health (Harber et al., 1989). Ultraviolet wavelengths range from 100–400 nm and are subdivided into UVC (200–280 nm), UVB (280–315 nm) and UVA (315–400 nm). The latter is comprised of UVA2 (315–340 nm) and UVA1 (340–400 nm; (de l'Eclairage, 1970). The majority of UVR reaching the earth's surface is UVA (96.65%); UVB makes up approximately 3.35%, while UVC is blocked by the Earth's atmosphere, principally the ozone layer (Diffey, 2002). Although artificial sources of UVR exist in many fields (e.g., arc welding, household compact fluorescent light bulbs, manicure lamps, and sunbeds), the principal source of UVR is the sun (Magnus, 1976, Diffey and Challoner, 1978, Harber et al., 1974, Coleman et al., 2010). Several factors influence the amount of UVA and UVB present on any given day; these factors include the season, longitude, latitude, time of day, weather, and altitude. UVA is consistently present from sunrise to sunset, whilst UVB peaks at noon. UVB has been shown to increase with altitude to a greater extent than UVA (Cutchis, 1980, Frederick et al., 1989).

In terms of exposure to solar radiation, there have been relatively few studies published on the impacts of outdoor exposure on photodermatoses with work tending to focus on eliciting responses with artificial sources to confirm the diagnosis. Comprehensive personalised studies into the amount of light a photosensitive patient is exposed to in their day-to-day life and how that will impact whether they develop their symptoms or not are lacking. Although there have been many studies regarding artificial ultraviolet light sources, their spectral emissions and their potential to impact human health, technological advances mean there is always the need for new research. The impact of UV sources on skin health has tended to focus on non-photosensitive patients therefore there are fewer publications examining the role of artificial UV sources on photosensitivity with the thresholds for developing reactions in real world situations poorly defined. One recent example is the phasing out of incandescent lamps and their replacement with compact fluorescent lamps. Due to a lack of testing in photosensitive conditions before widespread introduction, many photosensitive patients were potentially adversely affected (Fenton et al., 2014).

1.2.2 Action spectrum

The action spectrum measures the dose of radiation required to evoke a specific response at varying wavelengths, and it is considered a fundamental step in examining both normal and abnormal skin responses to different wavelengths of UVR and visible light. In 1922, Hausser and Vahle published their study on the action spectrum (Roelandts, 2007). Identifying an individual's action spectrum concerning photosensitivity is invaluable in the diagnosis and management of conditions, particularly in the case of DIP; (Young, 1997, Diffey and Farr, 1988).

1.2.3 Photochemical reactions

Photochemical reactions are processes, which convert chromophores into photoproduct molecules. Chromophores are any molecular element (amino acid, lipid, DNA) with the ability to absorb energy from UVR of various wavelengths (Douki et al., 2003, Sutherland and Griffin, 1981, Ziegler et al., 1994). Each chromophore has a distinctive absorption spectrum characterised by absorption peaks at specific wavelengths (Diffey and Kochevar, 2007). When a chromophore is exposed to UVR or visible light, it is converted from ground state to a singlet or triplet excited electron state (figure 1-2). Decay from the singlet state to the ground state releases energy in the form of heat or fluorescence; from the triplet state, decay energy may be transferred via a type I or type II reactions, yielding radicals such as hydroxyl radicals or peroxides. Superoxide formation may also take place. Type II reactions may occur when energy from the decay of the triplet to the ground state is transferred to molecular oxygen, yielding singlet excited state oxygen (Diffey and Kochevar, 2007, Cadet et al., 2014, Douki et al., 2003).

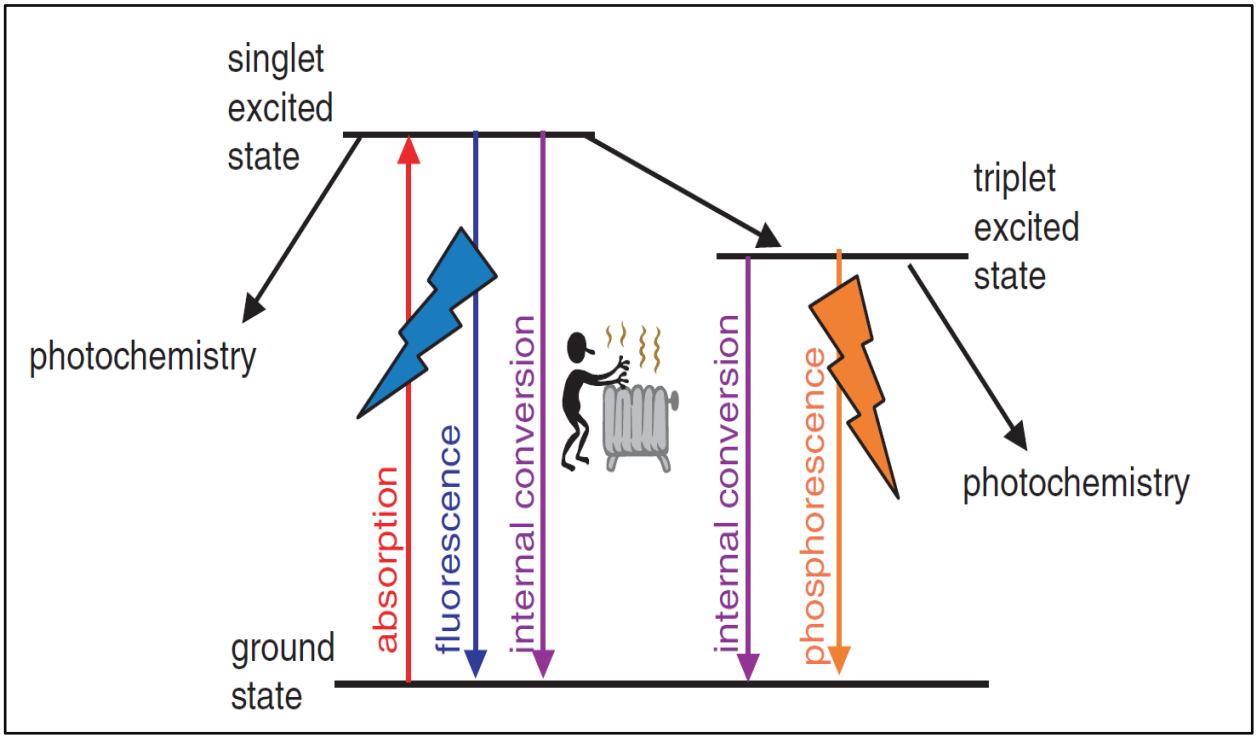


Figure 1-2 Photochemical reactions

The ground state molecule absorbs the energy of a photon to form an excited singlet state (red arrow). The excited singlet state then releases this energy as either light (fluorescence [blue], as heat (internal conversion [purple] and either undergoes a chemical reaction or converts into a triplet excited state. The triplet excited state releases energy as light (phosphorescence [orange]), heat (internal conversion [purple]), or undergoes a chemical reaction (including energy transfer). Adapted from (Lim et al., 2007a).

1.3 Effects of sunlight exposure on skin

Skin is the largest organ in the human body, and it has several functions: it plays a vital role in the body's protection against external physical, chemical, and biological effects; it protects the body from excessive water loss, and it plays a role in thermoregulation. It has been estimated that in a 70 kg person, the skin would weigh more than 5 kg and would have a surface area of 2 m^2. Human skin comprises three main layers: the epidermis, dermis, and a layer of subcutaneous fat. A layer of muscle is located beneath the subcutaneous layer, separating it from the body (McGrath et al., 2010). Skin structure layers comprise of epidermis, dermis and subcutaneous layers.

1.3.1 Epidermis

The epidermis is the protective outer layer of the skin and contains mainly keratinocytes, Langerhans cells, Merkel cells, and melanocytes. The epidermis consists of four main layers:

The *stratum basale* is usually one cell in thickness, but it can be two or three cells thick in the hyperproliferative epidermis and glabrous skin. It is responsible for the continuous replenishment of the more superficial epidermal layers. This layer is mainly comprised of dividing or non-dividing keratinocyte cells, and melanocytes which represent approximately 5–10% of the total cell population (Chu, 2008, Elder, 2014).

The *stratum spinosum* is made of polyhedral cells and is formed when cells start the differentiation process and move toward the surface of the tissue from the basal layer. These cells are connected by desmosomes and appear as prickles when viewed under a transmission electron microscope. Langerhans antigen-presenting immune cells also reside in this layer (Chu, 2008, Elder, 2014).

The *stratum granulosum* contains cells in stages of differentiation and contains Odland bodies, which are small lamellated cytoplasmic granules. The lipid components discharged by cells in the spaces between the cells play a vital role as barriers and provide cohesion between the cells in the outermost stratum corneum (Chu, 2008, Elder, 2014).

The *stratum corneum* is the top layer of the epidermis and is formed of terminally differentiated flat corneocytes cells, devoid of organelles and nuclei. The process of keratinocytes division and differentiation takes approximately 28 days; however, this duration can change as a result of different disease processes (Chu, 2008, Elder, 2014).

1.3.2 Dermis

The epidermis is connected to the dermis via a basement membrane; the dermal-epidermal junction, an intricate network of glycoproteins and proteins extending from within basal keratinocytes into the upper surface of the dermis. The dermis forms an internal junction with subcutaneous fat and an external junction with the epidermis, and its main function is to protect the body from mechanical injury. Its thickness varies greatly, from over 5mm on the back to less than 1mm on the eyelid. The dermis comprises various extracellular matrix molecules, such as collagen (providing tissue strength), elastin (made into fibres which provide elasticity), and glycosaminoglycans (ground substance) necessary for tissue hydration. The predominant cell type in the dermis is the fibroblast, responsible for collagen and elastin fibre synthesis (Chu, 2008, Elder, 2014, James et al., 2011).

1.3.3 Subcutaneous fat

A large percentage of the human body is made up of fat, approximately 80% of which is in the subcutis. The remaining 20% of fat in the body surrounds internal organs. Fat insulates, offers mechanical cushioning, and acts as a store of energy. Furthermore, it may also perform an endocrine function, for example, when it communicates with the hypothalamus through leptin or other secreted molecules to regulate appetite or energy change (James et al., 2011).

1.4 The skin and ultraviolet radiation

Upon hitting the skin, the light may be absorbed, reflected, or scattered. Reflection occurs at the epidermal surface, whilst scattering is principally seen in the dermis. The shorter wavelength UVB is absorbed by the epidermis and in the top layer of the dermis, whilst the longer wavelength UVA penetrates the dermis (Lui and Anderson, 2007), as shown in Figure 1 3. The skin contains many chromophores that can interact with UVR or visible light; these include amino acids, DNA, melanin, haemoglobin, lipids, porphyrins, and nucleotides. Exogenous compounds may also act as chromophores in the skin, for example, photosensitising drugs and tattoo pigments (Diffey and Kochevar, 2007). Each chromophore absorbs a specific range of wavelengths, leading to photochemical reactions and immune system activation. Examples of chromophores and their absorption spectrums are presented in Table 1-1.

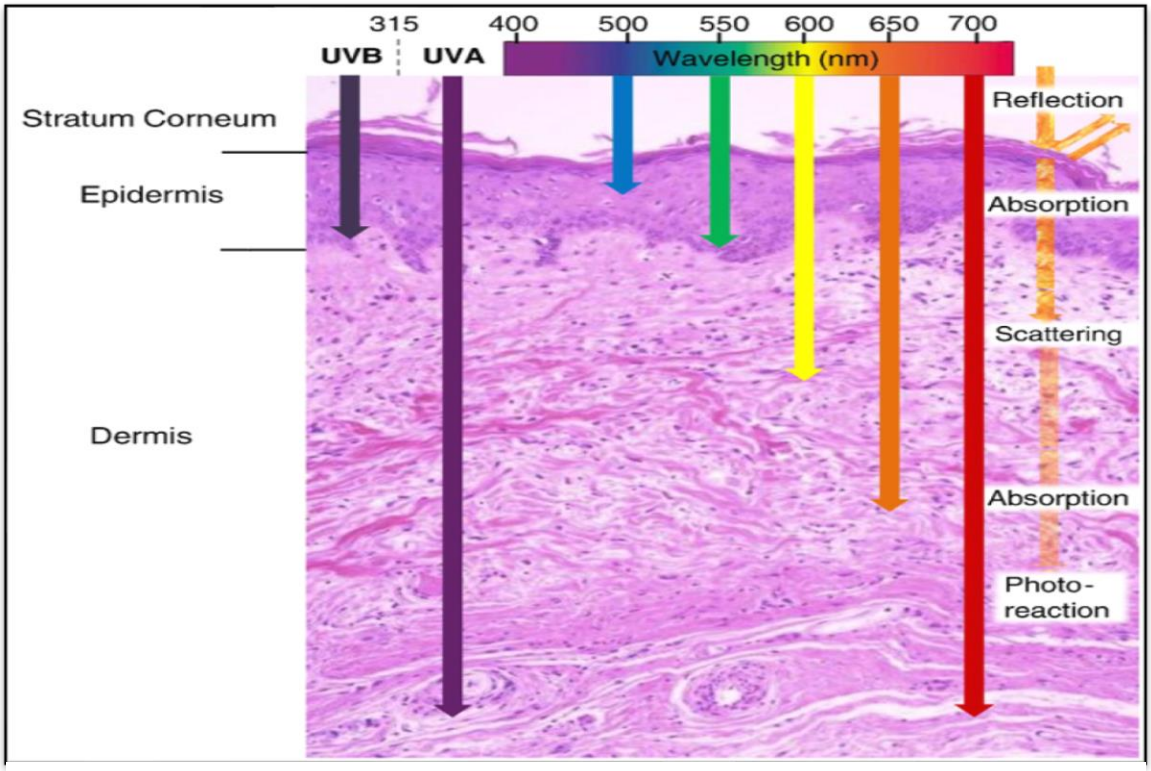


Figure 1-3 Light penetration in the skin.

The epidermis absorbs most of UVB while UVA penetrates deeper to reach the dermis. Adapted from (Matos and Sheth, 2016).

Table 1-1 Examples of endogenous skin chromophores, each chromophore has a specific absorption spectrum leading to photochemical reactions and immune system activation

Chromophore	**Absorption spectrum**	**References**
β-carotene	Absorption maxima at 465 and 490 nm in the visible spectrum. Also absorbs in the UVR range	(Mahmoud et al., 2008)
Protoporphyrin IX	Maximum absorption at 405 nm	(Mahmoud et al., 2008)
Pure DNA	The absorption peak at about 260 nm (UVC) with UVB (300 nm) and UVA (350 nm)	(Sutherland and Griffin, 1981)
Melanin	UVB, UVA and visible wavebands	(Kollias, 1995)

1.5 Light penetration and drug-induced photosensitivity

Acute adverse effects of UVR, such as a phototoxic reaction, will be visible in exposed areas where light can reach the skin. Sites that are naturally shaded, such as skin folds, behind the ears, and under the chin, are less likely to be affected as the light will not reach these sites. Different wavelengths of light penetrate to different depths in the skin as follows: UVA penetrates to the dermis and subcutaneous tissue, UVB penetrates to the epidermis, UVC penetrates to the stratum corneum, and visible light penetrates to the reticular dermis-subcutis layer (Tonnesen, 2004).

Chemical interactions between electromagnetic radiation (UVR or visible light) and photoactive drugs result in type I or type II reactions. These reactions generate reactive species (i.e., free radicals, superoxide, and singlet oxygen), which cause photodamage (Aloisi et al., 2007; Schuch et al., 2017). Chemical structures that are more likely to interact with light include aromatic ring-shaped planar molecules or conjugated double bonds containing nitrogen, sulphur, or oxygen (Tamat and Moore, 1983). Little is known regarding the impact of DIP on various skin layers, and further research is needed to explore this.

1.5.1 Sun-reactivity and skin phototypes

Fitzpatrick developed a classification for skin phenotypes in 1975, and this classification is widely used in the dermatology field. This classification is based on skin pigmentation and skin response to UVR exposure, for example, burning and tanning. This tool is considered crucial in the diagnosis and management of many photodermatoses. Table 1-2 and their response to different UVR wavelengths (Fitzpatrick, 1988).

The Fitzpatrick skin phototype classification system is a rapid, easy, widely used technique however it does have limitations. Fitzpatrick skin typing results are subjective and different results have been noted when the subject is asked to self-assess versus when the assessment is carried out by interview (Eilers et al., 2013, Liu et al., 2006). Similarly, the precise wording of the questions can significantly alter outcomes (Trakatelli et al., 2017). It has also been noted that it is not always clear whether subjects are considering single or multiple sun exposures in their responses (Ravnbak, 2010). In order to overcome the subjective nature of this skin typing system, techniques to objectively measure and classify skin type have been developed including, for example, minimal erythemal dose, minimal melanogenic dose (Wulf et al., 2010). It has been further suggested that the Fitzpatrick skin phototyping system is suboptimal in quantitating skin cancer risk and predicting post-inflammatory hyperpigmentation following cosmetic procedures hence further skin typing systems have been developed to address the skin typing requirements of particular fields (Gupta and Sharma, 2019). Assessment of the skin type can be carried using Different classification systems as shown in Table 1-3.

Table 1-2 Fitzpatrick clinical classification system for skin phototypes and their typical minimal erythema dose range

Phototype	**Sunburn & Tanning**	**UVA MED (mJ/cm^2)**	**UVB MED (mJ/cm^2)**
I	Easily burns Never tan	20–35	15–30
II	Easily burns Minimally tans with difficulty	30–40	25–40
III	Moderately burns Moderately & uniformly tans	40–55	30–50
IV	Minimally burns Easily & moderately tans	50–80	40–60
V	Rarely burns Profusely tans	70–100	60–90
VI	Never burns Profusely tans	100	90–150

Adapted with alterations from (Alam, 2004)

Table 1-3 Different classification systems that have been used for skin type assessment

Classification System	Method of Classification	Measurement and Utilization in Practice
Baumann skin type (Baumann, 2008)	Self-reported [a]	Classify skin type according to four different components: dry or oily, sensitive or resistant, pigmented or non-pigmented, and prone or tight.
Fanous classification (Fanous, 2002)	Self-reported [b]	Based on race and genetic origin of the patient (six categories: Nordics, Europeans, Mediterraneans, Indo-Pakistanis, Africans, and Asians); used for laser resurfacing, chemical peels, and dermabrasion.
Fitzpatrick skin type (Fitzpatrick, 1988, Sachdeva, 2009)	Visual, self-reported [a]	A six-point subjective classification system developed to assess the propensity of the skin to burn during phototherapy.
Glogau wrinkle scale (Glogau, 1994)	Visual	Photographs used to assess photoaging (rhytides and discolouration) in white individuals.
Goldman World Classification of Skin Types (Goldman, 2008)	Visual, self-reported [b]	Skin colour, response to burning or tanning, and post-inflammatory hyperpigmentation, based on race/ethnicity.
Kawada Skin Classification System for Japanese Individuals (Kawada, 1986)	Self-reported	Used to describe Japanese skin types and their sensitivity to UV light, sunburn, and tanning.
Lancer Ethnicity Scale (Lancer, 1998)	Self-reported [b]	Accounts for five different skin types based on geography and heredity; can be used in conjunction with Fitzpatrick skin type to assess for risk factors before treatments such as cosmetic laser surgery or chemical peels.
Modified Fitzpatrick skin type (Sharma et al., 2018)	Self-reported [a]	Modified to assess phototype, skin colour, and the ability to burn or tan in Indian individuals.
Roberts Skin Type Classification System (Roberts, 2008)	Visual, self-reported [b]	Four elements (phototype, hyperpigmentation, photoaging, and scarring) are evaluated to identify a patient's skin type and provide data to predict the skin's likely response to insult, injury, and inflammation.

Classification System	Method of Classification	Measurement and Utilization in Practice
Taylor Hyperpigmentation Scale (Taylor et al., 2005)	Visual	15 uniquely coloured plastic cards spanning the full range of skin hues; each card contains ten bands of increasingly darker gradations that represent progressive levels of hyperpigmentation.
Von Luschan chromatic scale (Treesirichod et al., 2014)	Visual	36 opaque glass tiles compared to the patient's skin to establish race classifications by skin colour.
Willis and Earles scale (Willis and Earles, 2005)	Self-reported [b]	Used in people of African descent to classify skin colour, UV light reaction, and associated pigmentary disorders.

Adapted with alteration from (Ware et al., 2020).

a Questionnaire, may or may not be modified.
b Detailed family history (ancestry).

1.5.2 Minimal erythema and dose standard erythema dose

The minimal erythema dose (MED) is defined as the lowest dose of UVR required to produce just perceptible erythema within 24 hours of irradiation with a given UV spectrum (Standard, 1998, Ouinn et al., 1994). The standard erythema dose (SED) is a unit of measurement defined as the dose of erythemal effective radiation of a defined standard set of wavelengths measured over an area of $1m^2$ with 1SED = 100 J/m^2. One way to express an MED would be to use the units of SED however the spectrum of the light source used would have to match the standard spectrum of the SED unit. The SED unit of measurement is used to standardise and allow comparison of exposures between different UVR sources, including natural sunlight. (Diffey et al., 1997).

1.5.3 Sunburn response

Acute exposure of human skin to UVR results in the sunburn response. Sunburn encompasses several different characteristics, including erythema, heat, pain, and swelling (Fitzpatrick, 1988, Harrison and Young, 2002). Erythema is the most common feature, becoming visible within 3–6 hours of exposure and peaking 18–24 hours after irradiation. The response can last as long as 72 hours (Diffey and Oakley, 1987, Farr et al., 1988). Furthermore, UVB-induced erythema is dose-dependent, whilst UVA-induced immediate erythema tends to resolve gradually over two to three days (Rhodes et al., 2001; Rhodes et al., 2009). UVB radiation exposure is typically associated with the sunburn response; UVA can induce similar skin erythema, however for this process to occur an approximately 1000-fold higher dose than UVB is required. Sunburn is associated with skin phototypes – Type I and Type II demonstrate the greatest vulnerability (Parrish et al., 1982, McKinlay, 1987).

The sunburn response is characterised histologically by a mixed dermal neutrophilic, and lymphocytic infiltrate (Hawk et al., 1988). TNF-α and IL-8 are upregulated in the epidermis of normal human skin after UVB exposure (Strickland et al., 1997). Keratinocytes may be an essential cell in the initiation of the UVB-induced inflammatory response, producing a significant range of cytokines and chemokines (Barker et al., 1991). The chromophore associated with the acute erythema response for sunburn is currently unknown. However, it has been suggested that it could be DNA (Young, 1997).

Ultraviolet radiation is detrimental to many tissue components, including nucleic acids, proteins, and phospholipids, as it may cause a number of different proinflammatory molecular responses.

The output of a number of different proinflammatory cytokines, such as tumour necrosis factor (TNF-α) and interleukin (IL)-1, IL-6, IL-8, and IL-12, may be produced by cells following UVR exposure. These molecules may play key roles in the different stages of UVR-induced inflammation, including transcription factor activation (especially IL-1, TNF-α), endothelial adhesion molecules induction, and leukocytes chemotaxis from the vasculature into the dermis (especially that demonstrated by IL-8, TNF-α) ((Kupper et al., 1987, Strickland et al., 1997, Oxholm et al., 1988).

1.5.4 Acute effects of ultraviolet radiation on the skin

Acute effects of UVR on the skin may cause several different reactions, some of which are detrimental to the skin's health in the short term or following long-term cumulative exposure. Other effects may provide benefits. The most commonly recognised short-term effects from UVR exposure include immediate pigment darkening, sunburn, tanning, vitamin D synthesis, the presentation of photosensitivity disorders, and immunosuppression (Krutmann, 2000, D'Orazio et al., 2013). UVB creates significant dermal effects, for example, inducing the release of mediators by epidermal cells, mainly the keratinocytes. It also has clear direct impacts on upper dermal cells and structures, such as fibroblasts and endothelial cells. Both UVA and UVB have indirect effects through the creation of reactive oxygen species (ROS), generated upon the absorption of UVR by endogenous photosensitisers (Young et al., 1991, Barker et al., 1991, Rhodes et al., 1996).

1.5.5 Pigment darkening & tanning

Skin pigmentation is a direct result of UVR exposure and can be seen in three different stages, namely immediate pigment darkening (IPD), persistent pigment darkening (PPD), and delayed tanning (D'Orazio et al., 2013).

Immediate pigment darkening

Immediate pigment darkening occurs as a direct result of low doses of UVA exposure (1–5 J/cm^2). However, these effects usually fade within 10–20 minutes. From a clinical standpoint, IPD is recognised by a grey-brown colour to the skin and may occur as a result of the oxidation and redistribution of pre-existing melanin without new melanin synthesis (Hönigsmann, 2002, Beitner, 1988).

Persistent pigment darkening

Persistent pigment darkening results from skin exposure to high doses of UVA (>10J/cm^2). This effect may be ongoing for 2–24 hours. Clinically, PPD skin appears as a brown colour and occurs as a result of further melanin oxidation and redistribution (Hönigsmann, 2002).

Delayed tanning of the skin

Tanning is a delayed response to UVR exposure, arising from increased numbers of melanocytes, upregulation of melanin synthesis, and enhancement of the tyrosinase enzyme (Stierner et al., 1989, Fitzpatrick et al., 1983). Delayed tanning is more apparent approximately 72 hours following exposure to UVR (Rhodes and Lim, 2007). Tanning can be induced by both UVA and UVB, although the latter is regarded as more efficient. Since UVB is more erythemogenic compared with UVA, the tanning induced by UVB may be preceded by erythema and may lead to an increase in the thickness of the epidermis. On the other hand, UVA may create tanning without any recognisable erythema. Sun-reactive skin types III and IV are recognised as demonstrating a greater ability to tan, whilst sun-reactive skin types I and II are less able to do so (Young et al., 1991).

1.5.6 Immunosuppression

Ultraviolet radiation can induce an immunosuppressive state in the skin, as evidenced by the downregulation of the delayed-type hypersensitivity (DTH) response (Duthie et al., 1999). Previously, immunosuppression was believed to be UVB-mediated, but recently UVA-mediated immunosuppression has been of increasing interest. This is clinically relevant when recognising the more significant proportion of UVA compared to UVB in sunlight (Schwarz and Halliday, 2007). Ultraviolet radiation-induced immunosuppression is a complicated phenomenon mediated by lymphocyte infiltration, keratinocytes, and endothelial cells (Rhodes and Lim, 2007). Following skin exposure to UVR, epidermal Langerhans cells (the key epidermal antigen-presenting cells) undergo modulation in their function and number, migrating from the epidermis to local draining lymph nodes. This reduces antigen presentation by Langerhans cells, leading to a reduction in immune responses. Moreover, UVR induces an abundance of CD11+ macrophages, which are immunosuppressive (Kang, Hammerberg et al., 1994).

UVR has a remarkable effect on skin lymphocytes, significantly reducing the number of T-helper cell type1 (Th1) cytokines. Interleukin-12 and gamma interferon (IFN-γ), which are known to mediate the contact hypersensitivity (CHS) and DTH immune responses, increase along with a rise in several immunosuppressive T-helper cell type 2 (Th2) cytokines, including IL-4 and IL-10. Hence, the responses of T-lymphocytes are reduced through IL-10 because antigen presentation is inhibited through antigen-presenting cells. Notably, IL-10 can be secreted by many cells, including T and B cells lymphocytes, monocytes, macrophages, and keratinocytes (de Vries, 1995; Grewe, Gyufko et al., 1995). Several mediators besides Th2 cytokines are seen to mediate immunosuppression, such as TNF-α, which plays a vital role in response to sunburn and enhances the migration of Langerhans cells from the skin Prostaglandin E2 (PGE2) is a significant sunburn erythema mediator and a mediator of immunosuppression. (Cumberbatch and Kimber, 1992).

1.6 Photosensitivity disorders

Photosensitivity disorders (photodermatoses) are a group of skin conditions, which are induced or exacerbated by different wavelengths of light and classified into four groups: immunologically-mediated photodermatoses, the most common condition in this group; drug and chemical-induced photosensitivity; photoaggravated dermatoses; and DNA repair disorders. Photosensitivity disorders are illustrated in Table 1-4 (Lim et al., 2007a, Millard and Hawk, 2002).

Table 1-4 Photosensitivity disorders (photodermatoses) are classified into four groups: immunologically-mediated photodermatoses, drug and chemical-induced photosensitivity, photoaggravated dermatoses and DNA repair disorders

Immunologically mediated (idiopathic) photodermatoses	**Drug- and chemical-induced photosensitivity**	**Defective DNA repair disorders**	**Photo-aggravated dermatoses**
· Polymorphic light eruption (PLE)* · Actinic prurigo (AP) · Hydroa vacciniforme (HV) · Solar urticaria (SU) · Chronic actinic dermatitis (CAD)	· Endogenous: Cutaneous Porphyrias · Exogenous: Phototoxicity & Photoallergy	· Xeroderma pigmentosum · Cockayne syndrome · UVR sensitive syndrome · Trichothiodystrophy · Bloom syndrome · Kindler syndrome · Rothmund-Thomson syndrome.	**Diseases usually exacerbated by UVR:** · Lupus erythematosus · Dermatomyositis · Darier disease · Pellagra · Rosacea · Smith-Lemli-Opitz syndrome **Diseases sometimes exacerbated by UVR:** · Atopic eczema · Psoriasis · Seborrhoeic dermatitis · Acne vulgaris · Cutaneous T-cell Lymphoma · Pemphigus · Pemphigus foliaceus (erythematosus) · Pityriasis rubra pilaris

*Also known as PMLE

1.7 Drug-induced photosensitivity

Drug-induced photosensitivity (DIP) is the cutaneous adverse reaction between either ultraviolet radiation (UVR) or visible radiation and a specific photosensitising drug, either topically or systemically. This reaction is usually classified based on the mechanism of action into photoallergic or phototoxic reactions (Kirshbaum and Beerman, 1964). If a patient experiences abnormal photosensitivity, it is essential to identify the chemicals or drugs responsible for the photosensitisation. When completing an analysis of the photosensitive site, attention should be directed toward all areas on the face as well as to any shadow sites, such as under the hair and behind the ears. Several factors can affect photosensitivity, such as drug dosage, the light spectrum and intensity, and skin phototype. A wide range of systemic treatments have been identified as photosensitising (Frain-Bell, 1985, Harber and Bickers, 1989). Consequently, it is essential to direct efforts toward clinical examination, a thorough review of the patient's history, and phototesting to formulate an accurate diagnosis. DIP can usually be managed by avoiding exposure to sunlight and discontinuing the culprit drug if that is possible (Ferguson, 2002).

1.7.1 Action spectrum

A drug's spectroscopic and molecular characteristic can predict the drug's photosensitising potential. Drugs with low molecular weight and aromatic halogen atoms are the most likely to be associated with photosensitivity (Verdel et al., 2009). It has been reported that most photosensitising drugs absorb light in the UVA region, which may extend into the visible spectrum (mainly 315–430 nm), while, in a minority of drugs, the absorption spectrum is in the UVB region. This may be explained by the fact that the UVA penetrates deeper into the dermis than UVB (Diffey and Farr, 1988, Hunter et al., 1970, Ferguson et al., 1985). Drugs classes and absorption wavelengths illustrated in Table 1-5.

Table 1-5 Drugs classes and absorption wavelengths. Most photosensitising drugs absorb light in the UVA region and may extend into the visible spectrum (mainly 315–430 nm). while, the minority of drugs, the absorption spectrum is in the UVB region

Main classes	**Photosensitising drugs**	**Predominant wavelengths**
Antibiotics	· Fluoroquinolones · Nalidixic acid · Tetracyclines (particularly demeclocycline and doxycycline) · Sulphonamides	· UVA /visible · UVA · UVA · UVA
Diuretics and cardiovascular agents	· Thiazides · Furosemide · Amiodarone · Quinidine	· UVB/UVA · UVA · UVA · UVB/UVA
Nonsteroidal anti-inflammatory drugs	· Naproxen · Tiaprofenic acid · Piroxicam · Azapropazone	· UVA · UVA · UVA · UVA
Calcium channel antagonists	· Nifedipine · Diltiazem · Amlodipine	· UVB/UVA · UVB/UVA · UVB/UVA
Psychoactive drugs	· Phenothiazines (chlorpromazine, thioridazine) · Protriptyline	· UVB/UVA · UVA
Photodynamic therapy agents	· Temoporfin · Photofrin	· Visible · Visible
Antifungals	· Griseofulvin	· UVA

Adapted from (Dawe and Ibbotson, 2014)

1.7.2 Post-drug cessation effects

Phototoxicity susceptibility would be expected to correlate with the half-life of the drug; however, there is significant variation from one drug to the next. For example, in the cases of quinine and thiazide-induced photosensitivity, the symptoms can continue for up to nine months after cessation. However, the drugs tend to be eliminated within only hours after cessation of the drug. In other cases, such as amiodarone or photofrin, the photosensitivity results from the presence of the photoactive molecule in the patient's circulation and skin. Furthermore, the elimination rate for psoralens and fluoroquinolones, which have been widely reported as photoactive agents, is fast, commonly, within a period of 1–2 days after discontinuing the drug, any greater degree of vulnerability to photosensitive reactions disappear (Lim, Hoenigsmann et al. 2007).

1.7.3 Prevalence

Prevalence of DIP shows variances from one drug to another; moreover, these variations may occur among individuals taking the same medication. However, determining the prevalence of DIP is quite difficult and is likely to be underestimated. Furthermore, geographic variations have a significant impact on the prevalence of DIP. In addition, other factors, including variable drug metabolism in different communities and different photoprotection approaches, also play a role (Dawe and Ibbotson, 2014). The prevalence of photoallergic reactions is lower than that of phototoxic reactions. Although aged individuals may have less exposure to sunlight, they are more vulnerable to DIP, as they tend to use a greater number of drugs for different conditions (Trakatelli et al., 2009, Gould et al., 1995). Table 1-6 shows the prevalence of DIP, as reported by different studies.

Table 1-6 Prevalence of drug-induced photosensitivity reported to be between 1.9% and 14.5% by different studies

Study	Prevalence of DIP	Reference
The study evaluated the photosensitivity in 203 patients in an American academic medical centre reported systemic drug-induced phototoxicity	7%	(Fotiades et al., 1995)
A retrospective study of 116 patients diagnosed with photodermatosis at Singapore skin referral centre	11.3%	(Khoo et al., 1996)
A study by Norwegian Medicine Control Authority reported 799 adverse drug reactions involving the skin and appendages of which 64 were classified as photosensitivity	8%	(Selvaag, 1997)
A study at a photodermatology referral centre, Greece, of 310 patients diagnosed with idiopathic photodermatoses	4.8%	(Stratigos et al., 2003)
A study by an Australian photodermatology clinic of 397 patients diagnosed with photosensitivity disorders	2.1%	(Crouch et al., 2003)
Study of 141 predominantly Asian patients attending a photodermatology clinic in Singapore	14.5%	(Wong and Khoo, 2005)
A study of 280 patients seen by a dermatologist at the Department of Dermatology, Henry Ford Hospital, Michigan	13.3% of African Americans 10.7% of Caucasians	(Kerr and Lim, 2007)
Evaluation of spectrum of photodermatoses in 362 “dark-skinned” individuals presenting at a tertiary referral centre (India Institute of Medical Sciences)	1.9%	(Wadhwani et al., 2013)
Study 118 patients at the dermatology department at a Tunisian teaching hospital. Describes the adverse cutaneous reactions and their epidemiologic characteristics.	DIP is the third commonest cause	(Chaabane et al., 2013)
Results of phototesting at a Dundee photobiology unit, Scotland	4%	(Dawe and Ibbotson, 2014)
Photobiology unit at Salford Royal Hospital	5.4%	(Alrashidi et al., 2020)

1.7.4 Pathogenesis

Two patterns have been described in the pathogenesis of DIP. Phototoxicity is considered to be more common than photoallergy (Epstein, 1962, Epstein, 1983). These reactions occur when UVR or visible light is absorbed by photosensitising agents, such as drugs or cosmetics products. UVR dosage plays a significant role in DIP responses in phototoxic reactions, with minimum radiation exposure leading to milder reactions. Photoallergic reactions are rarely affected by UVR doses (Epstein, 1972, Storck, 1965). Clinically, the differentiation between phototoxic and photoallergic reactions are challenging, but it is widely accepted that systemic agents can cause phototoxic reactions while topical medications may lead to photoallergic reactions (Storck, 1965, Khandpur et al., 2017). Table 1-7 shown in Table 1-7.

Table 1-7 The differences between the two patterns of drug-induced photosensitivity : phototoxicity and photoallergy reactions

Feature	**Photoallergy**	**Phototoxicity**
Incidence	Low	High
Pathophysiology	Immune-mediated mechanism of action (Type IV hypersensitivity reaction)	Direct tissue injury
Required dose of medication	Low	Standard dose high
Required dose of radiation	Low	High
Onset after light exposure	> 24 Hours	< 24 Hours
Clinical appearance	Eczematous	Exaggerated sunburn reaction with erythema, itching, and burning
Other manifestations		Lichenoid eruptions, pseudoporphyria, onycholysis, erythema multiforme, hyperpigmentation, and telangiectasia
Sensitisation required	Yes	No
Localisation	May spread outside exposed areas	Only exposed areas
Pigmentary Change	Unusual	Frequent
Histology	Epidermal spongiosis, exocytosis of lymphocytes, and a perivascular inflammatory infiltrate	Necrotic keratinocytes, predominantly lymphocytic and neutrophilic dermal infiltrate

Adapted with alteration from (Gould et al., 1995)

1.7.4.1 Phototoxicity reaction

The phototoxic reaction is a non-immunological, pathological reaction leading to tissue injuries within minutes or hours after taking medication and exposure to the sun. This reaction occurs when photolabile agents interact with light, resulting in the formation of ROS, superoxide anions, free radicals hydroxyl radicals, and singlet oxygen; causing damage to cellular proteins, lipids, and DNA; and triggering an inflammatory response (Urbach, 1997, O'gorman and Murphy, 2014, Foote, 2012, Pathak and Stratton, 1968).

1.7.4.1.1 Clinical manifestation

Cutaneous phototoxic reactions have different patterns, appearing as either an immediate burning sensation and urticaria or pigmentation, which may occur shortly after administration of the culprit drug. Notably, some drugs have a distinct reaction, as shown in Table 1-8. Body sites most commonly affected are forearms, anterior parts of the legs, the face, the dorsum aspect of the hands, the nuchal area, and the V area of the chest. Furthermore, a sharp demarcation can be observed between affected and non-affected skin (Gould et al., 1995; Khandpur et al., 2016).

Table 1-8 Examples of culprit photosensitisers and different patterns of cutaneous phototoxic reactions

Photosensitisers	**Skin reaction**
Porfimer sodium, amiodarone, chlorpromazine	Pricking/burning, immediate erythema, oedema, urticaria
Fluoroquinolones, chlorpromazine, amiodarone, thiazide diuretics, quinine, demeclocycline, doxycycline, voriconazole	Sunburn-type reactions
Psoralens	Erythema (late-onset) Blister (higher doses) Hyperpigmentation
Naproxen, nalidixic acid, demeclocycline, amiodarone, fluoroquinolone, voriconazole	Increased skin fragility Blister (pseudoporphyria)
Calcium channel antagonists	Telangiectasia on exposed site
Thiazide diuretics	Dermatitis response

Adapted from (Khandpur et al., 2016).

1.7.4.1.1.1 Exaggerated sunburn reaction

Clinically, phototoxicity reactions mimic exaggerated forms of sunburn reactions in association with skin erythema and oedema. Furthermore, there are significant variations in clinical presentation, depending on the source of light and drug dosage. Patients can be asymptomatic, experience a mild burning sensation on exposed skin, or develop severe symptoms, such as bullae and vesicles in association with skin burning and prickling (Epstein, 1983, Khandpur et al., 2017). It usually takes minutes to hours for the phototoxic reaction to develop, except for psoralens, where the reaction initiates 24 hours following contact and reaches its peak in 72–96 hours (Ibbotson and Farr, 1999).

1.7.4.1.1.2 Hyperpigmentation

Skin pigmentation may occur as a side effect of drug-induced phototoxicity. Hyperpigmentation reactions caused by different drugs illustrated in Table 1-9.

Table 1-9 Different patten of cutaneous hyperpigmentation reactions and culprit photosensitisers

Drug	**Hyperpigmentation reaction**	**References**
Amiodarone, chlorpromazine, clozapine, and imipramine	Slate-grey pigmentation	(Zachary et al., 1984, Waitzer et al., 1987)
Amiodarone and chlorpromazine	Golden-brown pigmentation	(Satanove, 1965)
Diltiazem	Slate-grey (lichenoid) reticulate hyperpigmentation	(Young et al., 1990)
Desipramine	Blue-grey photosensitive pigmentation	(Narurkar et al., 1993)
Silver	Blue-black pigmentation in sun-exposed areas	(Shelley et al., 1987)
Hydrochlorothiazide	Mottled hyper and hypopigmentation	(Masuoka et al., 2011)

1.7.4.1.1.3 Drug-induced pseudoporphyria

Porphyria is a condition caused by an enzymatic defect in the haem biosynthetic pathway, which leads to the release of phototoxic porphyrins in the bone marrow or liver. The distinctive ring shape of the porphyrin molecules enables the absorption of visible light (Moore and McColl, 1987, Harber et al., 1975). Furthermore, the structure of porphyrin molecules facilitates a rapid diagnosis of the condition, with porphyrins found in erythrocytes, plasma, stool, and urine (Lim and Peters, 1984). Acute porphyria is conditions that share similar photosensitivity, including porphyria cutanea tarda (PCT), hereditary coproporphyria, and variegate porphyria. Of these three conditions, PCT is the most common and can present clinically with cutaneous manifestation only and low levels of uroporphyrinogen decarboxylase (Elder et al., 1978). Type I PCT, also known as a sporadic subtype, is an acquired multifactorial condition, and it represents approximately 75% of all PCT cases (Aarsand et al., 2009, Kushner, 1982). Familial PCT is an autosomal dominant condition found in the remaining 25% of all PCT cases, and up to 90% of those patients are asymptomatic carriers (De Verneuil et al., 1978). Heredity coproporphyria and variegate porphyria have systemic and cutaneous symptoms. Clinically, the exposed sites, such as the face, neck, and back of the hands, are the areas mainly affected. An individual experiencing a large accumulation of porphyrin in the skin may also experience a condition known as bullous porphyria. Porphyrins are tetrapyrrolic molecules that absorb visible radiation in the 400 nm range (Whitcombe et al., 1991, Cacheux et al., 1994, Gouya et al., 1996). Cutaneous characteristics of drug-induced pseudoporphyria resemble those of PCT, including skin fragility and scarring, easy bruising, and milia-affected regions. Notably, the porphyrin profile remains normal (Al-Khenaizan et al., 1999). Several medications have been linked to drug-induced pseudoporphyria, namely naproxen, nalidixic acid, tetracyclines, sulfonylureas, furosemide, dapsone, benoxaprofen, tiaprofenic acid, and amiodarone (Gould et al., 1995, Al-Khenaizan et al., 1999).

1.7.4.1.1.4 Drug-induced cutaneous lupus erythematosus

Drug-induced subacute cutaneous lupus erythematosus (SCLE) linked to photosensitivity, with subacute cutaneous subtypes being the commonest. Clinically, drug-induced SCLE patients may present with small papular lesions with a scaly erythematous base, which can progress into psoriasiform plaques. These lesions are limited to photo-exposed areas, such as arms, face, neck, and upper part of the chest, and can heal without leaving scars (Gould et al., 1995). Phototoxic reaction in SCLE has been linked to calcium channel blockers, thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, and terbinafine. Furthermore, it is also linked to other drugs, such as antiepileptic; anticancer docetaxel, taxanes and paclitaxel; proton pump inhibitors; and TNF-α antagonists (Grönhagen et al., 2012).

1.7.4.1.1.5 Acute photosensitive dermatitis

Usually, patients experience an exaggerated sunburn reaction within 12–24 hours following sun exposure, which can appear clinically as well-demarcated, non-pruritic erythema with vesicle formations. Furthermore, epidermal desquamation and hyperpigmentation can follow initial signs (Gonçalo and Giménez-Arnau, 2015).

1.7.4.1.1.6 Photo-onycholysis

Photo-onycholysis involves the separation of the distal third of the nail from the nail bed. In addition, tenderness to pressure is noticed within two weeks of exposure to an offending drug. Drugs that have been reported to cause photo-onycholysis include quinine, clorazepate dipotassium, oral contraceptives, benoxaprofen, fluoroquinolones, mercaptopurine, chloramphenicol, psoralens, and tetracyclines (Baran and Brun, 1986, Tan et al., 1989).

1.7.4.2 Photoallergy mechanisms

A drug-induced photoallergic skin reaction is an immune-mediated response, usually a DTH reaction, requiring several exposures to the causative agent. Formation of a photo-antigen occurs via a haptenisation process, which involves the covalent binding of the causative agent to endogenous protein. Subsequently, the photo-antigen presents to dermal immune-competent cells, leading to the release of proinflammatory cytokines and chemokines and the formation of eczematous skin responses (Tokura et al., 1996b, Ohshima et al., 2000).

1.7.4.2.1 Clinical manifestation

Eczematous reactions are the main clinical features of photoallergic reactions and tend to be confined to sun-exposed skin. However, this reaction may spread to other sites in cases of repeated exposure. Clinically, the reactions can be acute, subacute, or chronic. In acute reactions, skin erythema in association with vesicles is the main presentation, while erythematous lichenified lesions are predominant in subacute or chronic reactions. Affected skin mostly resolves entirely after the culprit drug is stopped and light exposure avoided. (Gould et al., 1995; Lim et al., 1990).

1.7.4.2.1.1 Lichen planus-like reactions

Lichen planus-like reactions are drug-induced photoallergy. Manifestations may include scaly erythematous violaceous lesions in association with Wickham’s striae. Oral mucosae are not involved in this type of allergy (Frain-Bell, 1985; Gould et al., 1995).

1.7.5 Drugs commonly associated with drug-induced photosensitivity

1.7.5.1 Antiarrhythmics

1.7.5.1.1 Amiodarone

Amiodarone is an antiarrhythmic drug used to treat conditions such as ventricular tachycardia. It produces a dose-related photosensitivity reaction. The phototoxic reaction can be induced by both UVA and UVB. Classical clinical features of amiodarone photosensitivity reactions are a sudden onset of erythema with a tingling and burning sensation. Furthermore, a unique blue-grey skin pigmentation has been reported (Zachary et al., 1984, Harris et al., 1983, Ferguson et al., 1985). It has been reported that between 30-75% of patients using this medication experienced DIP (Chalmers et al., 1982, Harris et al., 1983, Rappersberger et al., 1989). Recovery from amiodarone phototoxicity usually occurs within months of drug withdrawal. However, prolonged reactions have also been recorded due to the prolonged drug elimination half-life (Yones et al., 2005).

1.7.5.2 Anti-hypertensive

Different classes of antihypertensive medication have been reported to cause photosensitivity reactions. In the first instance, diuretics are frequently reported as a leading cause of drug photosensitivity, whilst other classes, such as ACE inhibitors and calcium channel blockers (CCBS) have a significant effect in this regard. Anti-hypertensive drug and photoreactions presented in Table 1-10.

Table 1-10 Class and subclass of anti-hypertensive drug-induced photosensitivity reactions and cutaneous photoreactions

Class	Subclass	Photoreaction	References
Calcium channel blockers	· Dihydropyridine group: Amlodipine & nifedipine · Benzothiazepine group: Diltiazem	· Facial telangiectasia (photodistributed pattern, photodermatitis [a]) · Photodistributed hyperpigmentation, Dermatitis [a]	(Collins and Ferguson, 1993, Zenarola et al., 1991, Seggev and Lagstein, 1996, Grabczynska and Cowley, 2000, Boyer et al., 2003b)
Angiotensin-converting enzyme inhibitors	Ramipril, Quinapril Enalapril	Photosensitivity [a&b]	(Wagner et al., 2000, Rodríguez Granados et al., 2004, Kanwar et al., 1993a)
Beta-blocker	Tilisolol	Photosensitivity in one patient [a&b]	(Miyauchi et al., 1994)
Other antihypertensive	· Rilmenidine · Methyldopa	· Erythema and swelling (photodistributed pattern) in one patient · Photosensitivity [b] in one patient	(Mota et al., 1998, Vaillant et al., 1988)

a. Rechallenge test b. Photopatch test

1.7.5.3 Diuretics

Thiazide diuretics are a group of medications used to treat high blood pressure (hypertension). Hydrochlorothiazide is the most common diuretic of the thiazide group that is associated with photosensitivity (Monteiro et al., 2016b). Two further subcategories have also been identified, namely the loop diuretic furosemide and the sulphonamide-based thiazide molecules. The latter substances in this subcategory can induce a lichen planus-type response and a lupus erythematosus response (Johnston et al., 2002, Reed et al., 1985b). It has been reported that UVA or UVA and UVB wavelengths induce thiazide phototoxic reactions. Phototoxic skin reactions can present clinically as lichenoid skin lesions, dermatitis, severe sunburn reactions, or dermatitis of exposed skin (Addo et al., 1987; Johnston and Coulson, 2002). Moreover, chronic eczematous photosensitivity can persist for months to years, even following the withdrawal of the causative drug (Robinson et al., 1985).

1.7.5.4 Non-steroidal anti-inflammatory drug

Non-steroidal anti-inflammatory drug is prostaglandin synthesis inhibitors that have been reported to cause photosensitivity skin reactions. Piroxicam and benoxaprofen are the two main culprit medications in this group that have been reported to induce photosensitivity, although the latter is no longer available on the market (Drucker and Rosen, 2011). Celecoxib has also been reported to cause pseudoporphyria and photoallergic skin reactions (Cummins et al., 2000, Yazici et al., 2004). The most significant photosensitising capacity has been shown by naproxen, which usually causes pseudoporphyria (Levy et al., 1990). Topical NSAIDs can induce photoallergic reactions. In this group, mainly ketoprofen can cause severe symptoms, characterised by skin oedema and bullous formation or reactions similar to erythema multiforme (Matthieu et al., 2004).

1.7.5.5 Antibiotics

1.7.5.5.1 Fluoroquinolones

Fluoroquinolones are a group of broad-spectrum antibiotics that are used to treat both gram-negative and -positive infections. These drugs may cause significant phototoxic and photoallergic reactions that can limit their use (Ball and Tillotson, 1995, Ferguson, 1995, Johnson et al., 1997, Mehlhorn and Brown, 2007). The chemical progenitor of the first fluoroquinolone, that is the nalidixic acid group, is recognised as being a photosensitive molecule and may cause pseudoporphyria, PCT, and sunburn-like eruptions (Ferguson, 2003). The severity of clinical features varies and may include severe bullous eruptions as well as mild erythema on sun exposure sites (Lipsky and Baker, 1999, Vassileva et al., 1998a).

In addition, sparfloxacin has resulted in the occurrence of lichenoid reactions (Tokura et al., 1996a, Baran and Brun, 1986). Generalised erythematous subcorneal pustular drug eruptions have been reported with norfloxacin (Shelley and Shelley, 1988). Ciprofloxacin phototoxic reactions have been observed in cystic fibrosis patients (Burdge et al., 1995).

1.7.5.5.2 Sulphonamide

Sulphonamide derivatives have long been associated with photosensitivity (Epstein, 1939). Sulphonamide is an antibiotic that cannot cause photosensitivity by itself. However, derivative medications that contain sulphur, such as diuretics and anti-diabetic drugs, are common causes of photosensitivity (Vassileva et al., 1998a). Cotrimoxazole is a known photosensitiser due to its sulfamethoxazole component, which may lead to both phototoxic and photoallergic effects on skin exposed to sunlight (Zhou and Moore, 1997). The action spectrum of sulphonamide derivatives lies within the UVB and UVA wavelength (Ljunggren and Bjellerup, 1986). Photoallergic and, less frequently, phototoxic reactions have been reported following treatment with sulfacetamide, sulfadiazine, sulfaguanidine and sulfapyridine (Vassileva et al., 1998b).

1.7.5.5.3 Tetracycline

Tetracycline is a group of bacteriostatic antibiotics known to encompass several photoactive agents. As per available literature, phototoxic reactions are commonly reported for doxycycline and tetracycline (Drucker and Rosen, 2011). Tetracyclines have been reported to induce solar urticaria and onycholysis (Yap et al., 2000, Ibsen and Lasthein, 1982).

1.7.5.6 Other antibiotics

Several other antibiotics have been reported to cause DIP. Table 1-11 .

Table 1-11 Class and subclass of antibiotics and cutaneous drug-induced photosensitivity reactions

Antibiotics	**Subclass**	**Reaction**	**References**
Antituberculosis	Isoniazid pyrazinamide	Lichenoid eruption confirmed by PT & RC Photosensitivity confirmed by RC	(Lee and Jung, 1998) (Katiyar et al., 2010)
Sulfone antibiotic and anti-inflammatory agent	Dapsone	Phototoxic and photoallergic reaction, confirmed by RC and PT	(Joseph, 1987, Kar, 2008)
Third generation cephalosporins	Cefotaxime Ceftazidime	Increased susceptibility to sunburn. Photodistributed telangiectasia	(Borgia et al., 2000, Vinks et al., 1993)

Photopatch test (PT), Rechallenge test (RC)

1.7.5.7 Cholesterol-lowering agents

Statins are one of the most commonly used lipid-lowering drugs and are known to cause several different cutaneous reactions (Montanaro et al., 2008). Various medications in this group have been reported to cause photosensitivity. For example, simvastatin is known to cause prolonged photodistributed dermatitis. (Granados et al., 1998, Holme et al., 2002). Similarly, oedematous erythema in the sun-exposed areas can result from atorvastatin (Marguery et al., 2006). Moreover, photodistributed erythema multiforme has been caused by pravastatin as well as Simvastatin (Rodríguez-Pazos et al., 2010).

1.7.5.8 Antipsychotics

Phenothiazines are a group of antipsychotic medications that are used to treat psychosis symptoms such as delusions and hallucinations. Chlorpromazine and thioridazine are two drugs in the phenothiazines class that have been reported to induce photosensitivity reactions. This reaction is characterised by an immediate burning sensation with skin erythema, followed by another erythema attack within 24 hours. Furthermore, an exaggerated sunburn reaction can occur in individuals using chlorpromazine, and they may also experience bullous and lichenoid skin eruptions (Matsuo et al., 1979). Photodistributed slate-grey to violaceous hyperpigmentation can occur in patients taking high doses of both chlorpromazine and thioridazine over long periods (Satanove and McIntosh, 1967). This pigmentation tends to reverse on termination of drug use; however, the reversal effects might not be observed for many months.

1.7.5.9 Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are a group of medications that are used to treat various conditions, including depression, obsessive-compulsive disorder, and prophylaxis for migraines. Imipramine is a drug in this group that has been reported to induce photosensitivity reactions, presenting clinically as erythema in a photodistributed pattern. Furthermore, patients may experience slate-grey hyperpigmentation following prolonged sun exposure (Sicari et al., 1999, Walter-Ryan et al., 1985).

1.7.5.10 Selective serotonin reuptake inhibitors

These medications have been commonly used as antidepressants, and some drugs in this group are reported to induce photo-induced drug eruptions (PIDEs). Patients treated with escitalopram reported having erythroderma following artificial tanning (Ram-Wolf et al., 2008), whilst blister formation and erythema have been reported in patients treated with fluoxetine (Gaufberg and Ellison, 1995a).

1.7.5.11 Anxiolytics

1.7.5.11.1 Benzodiazepines

This is a group of medications that can be used to treat a variety of conditions, including anxiety, epilepsy, and seizure disorders. Alprazolam is a drug in this group that has been reported to induce erythema and pruritus in the exposed skin (Kanwar et al., 1990). Eczematous reactions have been reported with chlordiazepoxide (Luton and Finchum, 1965).

1.7.5.12 Antifungal drugs

1.7.5.12.1 Voriconazole

Voriconazole is an antifungal medication in the triazole class that is used to treat various fungal infections. It has been reported that voriconazole photosensitivity usually occurs in immunocompromised patients on long-term prophylactic therapy. Voriconazole photosensitivity reactions usually present as a classical phototoxic reaction that can present months after starting the medication, sometimes also resulting in pseudoporphyria and cheilitis (Drucker and Rosen, 2011, Frick et al., 2010, Tolland et al., 2007). Several studies reported that photoaging, squamous cell carcinoma, and melanoma can develop in skin sites that had previously experienced photosensitive reactions (Racette et al., 2005, Miller et al., 2010, McCarthy et al., 2007, Cowen et al., 2010).

1.7.5.12.2 Other antifungals

Itraconazole is a triazole antifungal medication that has been linked to photosensitivity that showed a positive phototoxic reaction after a rechallenge test (Alvarez-Fernández et al., 2000). Phototoxic dermatitis has been reported as a side-effect of ketoconazole, which is an antifungal in the imidazole group (Mohamed, 1988).

1.7.5.13 Proton pump inhibitors

Proton pump inhibitors are a group of medications that include omeprazole, lansoprazole, pantoprazole, and rabeprazole. These medications inhibit the proton pump function (H+/K+ ATPase) and suppress gastric acid production (Richardson et al., 1998). Photoallergic dermatitis after treatment with esomeprazole has been reported in a single case report (Shukla et al., 2010).

1.7.5.14 Quinine

Quinine can be used to treat malaria and muscle cramps, and it is also added to tonic water. It was reported to induce both photoallergic and phototoxic reactions. Phototoxicity is induced by UVA wavelengths (Wolf et al., 1987). The clearance half-life is typically between 10–12 hours, and this may be affected by smoking and age. Clinically, patients may present with eczematous or lichenoid phototoxic reactions (Dawson, 1986, Thomas and Munro, 1986).

1.7.5.15 Antineoplastic agents

Various antineoplastic medicines have been reported to induce photosensitivity skin reactions. Table 1-12 .

Table 1-12 Class and subclass anti-neoplastic drugs reported causing cutaneous drug-induced photosensitivity reactions

Main class	Subclass	Reaction	References
Tyrosine kinase inhibitor (TKI)	Vandetanib	Photodistributed erythematous and bullous eruption	(Chang et al., 2009)
Antimetabolites	Fluorouracil Hydroxyurea	Photosensitive eruptions, photodistributed hyperpigmentation Photodistributed granulomatous reaction.	(Falkson and Schulz, 1962, León-Mateos et al., 2007)
Plant alkaloids	Paclitaxel	Photodistributed erythema multiforme & onycholysis	(Cohen, 2009, Hussain et al., 2000)
Antiandrogens	Flutamide	Photosensitivity with positive photopatch and rechallenge test	(Martín-Lázaro et al., 2004, Yokote et al., 1998)

1.7.5.16 Miscellaneous medications

Several medications have been reported to cause various drug-induced photosensitivities. Table 1-13 Miscellaneous medications (class and subclass) reported causing drug-induced photosensitivity.

Table 1-13 Miscellaneous medications (class and subclass) reported causing drug-induced photosensitivity reactions

Main class	Subclass	Reaction	References
Oral retinoid	Etretinate	Increased susceptibility to sunburn & photoleukomelanoderma	(Ferguson and Johnson, 1989, Seishima et al., 2010)
Hormonal contraceptives	A contraceptive patch containing norelgestromin and ethinylestradiol	Erythematous vesicular eruption	(Gómez-Bernal et al., 2010, Cooper and George, 2001)
Antihistamine	Ranitidine Mequitazine Repirinast	Papulosquamous eruption. Positive PT Solar urticaria	(Kondo et al., 2000, Kim et al., 1995, Kurumaji and Shono, 1994)
Antiepileptic	Carbamazepine	Photosensitive lichenoid eruption, Positive PT & RC	(Yasuda et al., 1988)
Sulfonylurea oral hypoglycaemic agent	Glibenclamide	Eczematous photodermatitis PT: increased sensitivity to UVA & UVB	(Drucker and Rosen, 2011)
Antiplatelet agent	Clopidogrel	Photodistributed Lichenoid eruption, positive RC	(Dogra and Kanwar, 2003)
Disease-modifying antirheumatic drugs	Leflunomide	Photodistributed lichenoid eruption	(de Gutierrez and Abaca, 2004)
Aminosalicylate anti-inflammatory	Mesalazine	Bullous eruptions	(Horiuchi and Shimakura, 1999a)

Photopatch test (PT). Rechallenge test (RC)

1.8 Clinical evaluation of cutaneous photosensitivity

1.8.1 Clinical history

To make the correct diagnosis, a complete medical history of the patient should be obtained, an extensive cutaneous examination performed, and, if appropriate, phototesting should be undertaken. In addition, a laboratory examination should be conducted to exclude any systemic disease, for example, an antinuclear antibodies (ANA) panel screen, a plasma porphyrin profile screen, and histopathology of skin biopsy samples. In the Photobiology Unit at Salford Royal Hospital, the patient's evaluation takes four visits to be completed. Table 1-14 Photoinvestigation steps followed in the Photobiology Unit at Salford Royal Hospital.

Table 1-14 Photoinvestigation steps followed in the Photobiology Unit at Salford Royal Hospital

Day 1 (Monday)	· History and physical examination · Photoprovocation testing with the solar simulator and broadband UVA · Application of duplicate sets of potential photoallergens · MED testing narrowband UVB, UVA, and visible light · Blood and urine sample collection
Day 2 (Tuesday)	· Detailed examination of provocation testing sites and reading of the MED by a photobiology consultant dermatologist · A repeat of photoprovocation testing to the solar simulator and broadband UVA · Exposure of a single set of photoallergens to broadband UVA light
Day 3 (Wednesday)	· Third and final photoprovocation testing to the solar simulator and broadband UVA · Specialist patient education in photoprotection · Completion of the DLQI questionnaire by patient
Day 4 (Thursday)	· Detailed examination of the patients by the consultant and multidisciplinary team · Consultation with specialist photobiology consultant · Clinical photography and skin biopsy if required

1.8.2 Seasonal variations and time between sun exposure and lesions appearance

Knowledge of seasonal variations and the time between sun exposure and the onset of the reaction can assist in diagnosing drug-induced phototoxicity. Typically, DIP is characterised by only brief exposure to UVR, with symptoms persisting for several days and occurring in any season.

1.8.3 Window glass

A detailed history of the ability of window glass to filter sunlight may provide significant information regarding the provocation action spectrum of a photodermatosis, as typically UVA penetrates non-laminated window glass whilst UVB does not. Visible light always passes through the glass, unless the glass is opaque (Tuchinda et al., 2006).

1.8.4 Family history

Family history helps distinguish DIP from other photodermatoses, such as hereditary porphyria. Furthermore, positive family history has also been reported in actinic prurigo and PLE patients (McGregor et al., 2000). A family history of autoimmune or connective tissue diseases is crucial because it may be linked to photoaggravated dermatoses (Callen, 1999).

1.8.5 Clinical findings

The distribution of lesions in sun-exposed sites should be examined closely in the physical assessment of the patient, such as the cheeks, the forehead, the V-region or nape of the neck, the dorsum of the hands, and the extensor parts of bilateral forearms. The sun-protected regions, such as the upper eyelids, nasolabial folds, posterior auricular parts, periorbital sites in patients who wear glasses, the superior parts of the pinna (that may be hidden by the hair), and the submental area of the neck may be spared (Frain-Bell, 1985). Clinically, DIP can present with different morphological lesions; photoallergy reaction can present as eczematous eruptions, whilst phototoxicity can present as an acute inflammatory response with vesicles and bullae (Choi et al., 2014).

1.9 Photoinvestigation

Photosensitivity disorders can be diagnosed by phototesting. Phototesting is a process in which the skin is exposed to known doses and wavelengths of UVA, UVB, and visible light, after which the irradiated skin is observed and assessed. Narrowband UVB, UVA, and visible exposure at specific wavelengths can be used to determine the action spectrum. The irradiated skin is examined 24 hours after exposure to determine the MED. The MED can be an essential tool in discriminating among different photodermatoses (Lim et al., 2007a).

1.9.1 Monochromator phototesting

Narrowband (monochromator) testing is a test that is used for the estimation of MED response. This test is performed by exposing the patient's back to increasing doses of UVA, UVB, and visible light from the left to the right side, then recording the MEDs 24 hours after exposure. Characteristic response patterns can then be linked to different photodermatoses (Haylett and Rhodes, 2009).

1.9.2 Photopatch testing

Clinically, several photodermatoses can present with an eczematous reaction pattern; photopatch testing can distinguish these conditions from other photodermatoses. To diagnose contact photoallergy, a photopatch test is essential. Patients with photoallergic contact dermatitis are evaluated through photopatch testing (PT). This method is similar to a general patch testing, which is conducted to assess allergic contact dermatitis, with the addition of UVR irradiation of the patch sites. A double set of photoallergens are applied to the patient's back, and the area is covered with an opaque material to protect from exposure to light (Bruynzeel et al., 2004). After 24 hours, one panel is irradiated using a dose of 50% MED-A or 5 J/cm^2 of UVA, whilst the other panel functions as the control. The use of the broadband UVA light source is recommended (Group, 1997). There are significant variations in the UVA doses used, but it is generally recommended to use 5 J/cm^2 for routine PPT (White, 1983, Thune et al., 1988, Hölzle et al., 1991, DeLeo et al., 1992, Duguid et al., 1993, Bell and Rhodes, 2000, Neumann et al., 1994, Choi et al., 2014). Responses are evaluated at 24 and 48 hours following exposure to the allergens. Further post-irradiation readings at 72 and 96 hours may be recorded to identify and assess allergic and non-allergic mechanisms of the eruption (Neumann et al., 1994, White, 1983).

1.9.3 Provocation light testing

The provocation testing allows the clinician to examine the eruption in response to a fixed dose of light under controlled conditions. Ideally, repeated exposures of body sites (forearm and back) are used as a single exposure may not be sufficient to evoke a response. The same area is exposed for three to four consecutive days. Typically, the starting dose is 80% of the MED, which is increased by 10% to 20% over the following days (Choi et al., 2014, Lim et al., 2007a).

1.9.4 Laboratory tests

A series of laboratory investigations are conducted to aid in diagnosis. Connective tissue disease screening can be done to diagnosis SLE. Urine and blood samples can be scanned for porphyrin fluorescence to confirm the diagnosis of porphyria (Cohen and Lim, 2000). If the porphyrin screens are positive, further chemical analyses of urine, blood, and even faeces are conducted to identify and confirm the type of porphyria. Human leukocyte antigen (HLA) typing has been reported to be associated with AP (Grabczynska et al., 1999, Spencer et al., 1996), Immunoglobulin E (IgE) reveals atopy, while vitamin D status can be low due to sun avoidance (Farrar et al., 2013).

1.9.5 Dermatology life quality index

Skin conditions can have a substantial impact on patients' lives, affecting social relationships, everyday activities, and mood status. The DLQI, a questionnaire comprising ten questions was designed to capture information on the impact of different skin conditions on patients' lives. Initially developed in 1994 (Finlay and Khan, 1994), the questionnaire has been used to provide information regarding the impact on the quality of life of a range of conditions, including psoriasis (Loft et al., 2019), eczema (Nagpal et al., 2019), and chronic urticaria (Itakura et al., 2018). The DLQI has been validated and translated into many languages (Lewis and Finlay, 2004). The DLQI questions require patients to reflect on the impact of their skin conditions over the last week. Each response is scored from zero to three, where three is the highest impact and zero the lowest. All responses are then added to provide a maximum possible score of 30. A method of banding the DLQI scores has allowed further interpretation of the responses (Hongbo et al., 2005), as follows: 0–1, 'no effect on QoL'; 2–5, 'small effect'; 6–10, 'moderate effect'; 11–20, 'large effect'; and 21–30, 'extremely large effect'. Although DLQI is a simple validated, scoring system that has been used to assess the impact of QoL on skin-related conditions (Finlay and Khan, 1994). It has been criticised for its reduced capacity to capture emotions and mental health effects of some dermatological conditions (Badia et al., 1999, De Korte et al., 2002). Both *et al.*(2007), highlighting the inability of DLQI to fully capture the emotional impact photodermatoses on patients' QoL (Both et al., 2007). The severity of a photodermatosis is affected by several variable factors for example recent sun exposure, climate conditions and season. DLQI is unable to capture the full impact of these factors on the patients OoL as it asks the patient to only review their experiences 'over the last week'. A patient's experiences may be very different on an over last week in midwinter versus a sunny midsummer's week. A patient may have had no symptoms of their photodermatoses but in order to achieve this, they may have had to remain indoors with the curtains drawn for months on (Rutter et al., 2020). The psychological impact of behavioural avoidance of trigger factors, for example, by avoiding social gatherings outdoors, family holidays and shopping during daylight hours may have a significant high impact on patients QoL which has not been captured by DLQI (Rutter et al., 2020, Jong et al., 2008). Photosensitivity symptoms, unlike other skin conditions, fluctuate with season and ambient UVR or visible light level, meaning that questionnaires that focus only on the last week may underestimate the impact.

Therefore, patients may be asked to complete two questionnaires, considering impact over both the last week and the last year. This approach has been used in previous studies involving photosensitivity (Rizwan et al., 2013, Haylett et al., 2018).

1.10 Management of Photosensitivity

Photoprotection is a vital step in the management of all photodermatoses. Various factors can protect skin against UVR; for example, environmental factors, such as fog, clouds, and ozone may act as natural photoprotective agents. An awareness regarding avoidance of exposure during the times when the sun is at its maximum, which is from 10 am to 4 pm, is also essential. Physical photoprotective agents, including specific clothing, laminated window glass (in homes or cars), sunscreen, and even makeup can be important aspects of photoprotection measures. In addition, using sunscreen that can provide protection against the responsible action spectrum is an important measure. Photoprotective measures will be mentioned in detail in the following sections.

1.10.1 Photoprotection

1.10.1.1 Clothing

Clothing is one of the physical photoprotection agents that plays a vital role in photoprotection. The ‘UVR protection factor’ (UPF) is used to measure a fabric’s protection level against UVR; it is the equivalent of the sunscreen SPF (Kullavanijaya and Lim, 2005), with UPF reflecting the efficacy of fabric protection against UVB rather than UVA. The European Committee for Standardisation recommended that clothing UPF level should be 40 and have the ability to transmit less than 5% of UVA and, if it meets this standard, to be labelled EN13758-2 (Gambichler et al., 2006). Clothing protection against the sun is affected by various factors, such as fibre material, the density of the weave, and chemical processing (Hatch and Osterwalder, 2006). In addition, it has been reported that darker colour fabrics have a higher UPF as compared to lighter colour fabrics (Wang et al., 2001). Table 1-15 shown in Table 1-15.

Table 1-15 The sun-protectiveness functions of garments is affected by various factors; fibre material, the density of the weave, and chemical processing

Factors decrease UVR transmission	Factors increase UVR transmission	References
· Tightly woven fibres · Thick fabrics · Wool and polyester fibres · Dark coloured fibres · Shrinkage after laundering · Additives added to washed fabrics · UVR absorber	· Bleaching · Fabric stretching · Chemical processing (such as desizing) · Removing agents (such as starch)	(Davis et al., 1997, Crews et al., 1999, Wang et al., 2001, Sinclair and Diffey, 1997) (Sarkar, 2007, Gambichler et al., 2002)

Adepte from (Lim et al., 2007b)

1.10.1.2 Sunscreens

Sun protection factor (SPF) is determined by the use of a defined scientific method to evaluate the level of protection provided by the sunscreen. SPF is estimated from the MED of sunscreen-protected skin versus the MED of unprotected skin. SPF estimates protection against UVB (Food and Administration, 1978).

Sunscreens (organic and inorganic)

Sunscreens can provide anti-UVR protection if applied liberally. Nevertheless, applying sunscreen at the start of the day does not mean it is safe to increase exposure to the sun, so repeated application every two hours is recommended to achieve maximum protection (Lademann et al., 2005). There are two types of topical sunscreen filters, namely organic and inorganic agents, formerly designated as ‘chemical’ and ‘physical’, respectively. It has been reported that organic and inorganic ultraviolet filter materials work to operate synergistically to enhance SPF effects (Kullavanijaya and Lim, 2005).

Inorganic agents

Inorganic agents work by forming an opaque layer of inert metal particles that reflect and scatter UVR and visible light radiation, for example, titanium dioxide and zinc oxide (Mitchnick et al., 1999). The main principles of sun protection for these agents are that they may reflect and absorb UVR, but they also form a protective shield against the visible light (Moseley et al., 2001).

Organic Agents

Organic sunscreens work by absorbing UVR, which, in turn, leads to a change in the state of the electron from a ground state to an excited state. Thereafter, the electron returns to a stable state and radiates trivial amounts of heat or fluorescent radiation. Organic sunscreens can be UVA, UVB or broadband absorbers. Ideally, these agents should be able to withstand sunlight, remaining photochemically stable after sunlight exposure, should not be affected by perspiration or swimming, and be non-allergenic, non-irritable, and non-toxic to the skin (Lautenschlager et al., 2007, Roelandts, 1998).

1.10.1.3 Window glass and windshields

Typically, window glass filters UVB whilst transmitting visible light and UVA; however, glass technology is a developing field, and new developments have led to an increase in the efficacy of glass to filter UVA1 and UVA2. Laminated glass is used to make windshields that can restrict UVA to a large extent. Different types of glass are used in buildings and cars, thereby offering various UVR protection properties that are determined by the glass type. Darkly tinted glass is the most appropriate option to protect against visible light (Kullavanijaya and Lim, 2005), while amber window film offers protection for EPP patients (Hathaway and Sliney, 2002).

1.10.1.4 Hats

Hats are the best way to safeguard the neck and the head, with the extent of protection depending upon edge width, fabric weave, and material (Kullavanijaya and Lim, 2005). It has been reported that a hat brim size can affect the level of sun protection, for example, hats with 7.5cm circumference providing an SPF of 5 for the neck area and 7 for the nose, while smaller hats provide minimal protection (Lyde and Bergstresser, 1997).

1.10.1.5 Makeup

Cosmetic facial foundation makeup contains pigments that can provide photoprotection of SPF 2–6 and can last for approximately four hours. To increase the photoprotection level, organic and inorganic filters should be added to the makeup; this would increase the SPF level to 15 or higher (Draelos, 2001).

1.10.1.6 . Specific treatments

1.10.1.6.1 Treatment of photodermatoses

Photodermatoses management can be challenging; photoprotection measures are fundamental. Various approaches to treat photodermatoses summarised in Table 1-16.

Table 1-16 Photodermatoses have various treatment measures; first-line therapy which includes topical and systemic therapy and second-line phototherapy

Condition	**First-line therapy**	**Second-line therapy**
Polymorphous light eruption	· Topical/systemic corticosteroids · Photoprotection · Immunosuppressive therapy	NB-UVB or PUVA
Chronic actinic dermatitis	· Photoprotection · Immunosuppressive therapy	Low-dose PUVA
Actinic prurigo	· Photoprotection · Thalidomide	NB-UVB or PUVA
Hydroa vacciniforme	· Photoprotection · Immunosuppressive therapy	NB-UVB or PUVA
Solar urticaria	· Antihistamines · Photoprotection · Omalizumab	Low-dose UVA or PUVA

NB-UVB: Narrow band UVB phototherapy. PUVA: Psoralens and UVA photochemotherapy. Adapted from (Lim et al., 2007a, Bylaite et al., 2009)

1.10.2 Management of drug-induced photosensitivity

The key steps in the management of DIP are to identify the photosensitiser and the responsible action spectrum. In most patients, discontinuing the culprit drug is the most effective step. In some cases, avoiding the responsible agents is impossible, so photoprotective measures, such as avoiding sunlight, wearing protective hats and clothing, and using sunscreen must be followed. DIP is managed mostly by withdrawing a drug as soon as the reaction is diagnosed and the drug identified (Drucker and Rosen, 2011). Even though phototoxicity susceptibility would be expected to correlate with a drug's half-life, there are significant variations from one drug to another. For example, quinine and thiazide-induced photosensitivity effects can last for up to nine months, even though the drugs tend to be eliminated from the blood within hours (Lim et al., 2007). Photoallergic reactions can extend for up to three weeks before subsiding (González and González, 1996). Using topical or systemic corticosteroids can stop the chronicity of conditions; a short-term course of oral prednisone (1 mg/kg) can be used for severe DIP reactions (Bylaite et al., 2009).

1.10.3 Hypotheses and aims

The principal hypotheses of the first project were: a proportion of patients who referred for photoinvestigation at the Photobiology Unit at Salford Royal Hospital have photosensitivity due to DIP. Further, there will be differences in the phototesting results of patients who were on different types of medications. Finally, DIP will have a significant impact on patients' quality of life. The second project hypothesis was that within the wider community there would be a considerable number of people who have undiagnosed DIP. Furthermore, the questionnaire can be used as a screening tool to identify these patients.

First project aims were to estimate the prevalence of DIP in patients referred to photoinvestigation at Photobiology Unit (Salford Royal NHS Foundation Trust) between 2000 and 2016. Further, to identify and classify the most frequent culprit drugs for the patient diagnosed with DIP. The key phototesting results associated with the most common culprit drugs were collected and reviewed to identify typical responses. Additionally, where available, the results of DLQI questionnaires were collected to determine the impact of DIP on patients' quality of life.

The second project aims were first to estimate the prevalence of DIP in the wider community. This was done by approaching the individuals attending the outpatient department at Salford Royal NHS Foundation Trust, Manchester, UK and asked them to complete a questionnaire which previously developed within the Photobiology unit. Second, identifying the demographic characteristics of the participants who found to take potential photosensitisers. Third, to classify the participants who were taking potential photosensitisers into unlikely, possible and probable cases of DIP. Finally, to determine the most common culprit drugs that can lead to probable cases of DIP.

Chapter 2: Methods and materials

2.1 Project 1: Prevalence of drug-induced photosensitivity in patients undergoing photoinvestigation

2.1.1 Study design

The study conducted from a review of the case notes of patients diagnosed with DIP at the Photobiology Unit, Salford Royal NHS Foundation Trust, Manchester, UK, between 2000 and 2016. The patients were first assessed and referred by general dermatologists from different centres in the UK: Northern and Central England and Wales. The case notes comprised a summary letter from the consultant photobiologist, where a standardized pro forma was used detailing a patient history and clinical assessment. Key information was extracted from the case notes and used to determine the drugs most frequently associated with DIP. The diagnostic monochromator and broadband phototesting were performed. Additionally, photopatch with control patch testing was performed. Detailed information regarding how the condition affects patients' QoL was collected using the DLQI. Laboratory tests result including connective tissue disease (CTD) screen, urine and blood porphyrin testing and serum 25-hydroxyvitamin-D (25OHD) level were also performed.

2.1.2 Patient clinical assessment

Patients attended the photobiology unit for four days. On the first day, a detailed clinical history was obtained by a specialist photodermatologist, with data collection including the patient's age, sex, and Fitzpatrick skin type classification; past medical history included the age of onset of skin condition; lesion morphology and distribution; associated symptoms; and; number of episode per year seasonal variation. Additionally, family and occupation history. History of photoprotective measures used, such as window glass; sunscreen and whether the patients felt they were effective, was also included. Questions regarding the patient's tendency to burn or tan provide an indication concerning skin type, and responses to more specific questions regarding the skin's response to midday sun exposure in June without any sun protection measures were also collected. Patients were encouraged to bring photographs of their skin lesions on the first visit.

2.1.3 Culprit drug

Many patients were taking multiple medications, which, in some cases, included several potential photosensitisers. A comprehensive drug history, including both medications taken at the onset of symptoms and current medication and start and stop date, was collected. Particular attention was paid to the relationship between drug treatment start dates and the onset of the clinical symptoms. In addition to prescribed medicines, details of any over the counter and herbal remedies used were also gathered. In all cases, culprit drug, according to the analysis, was identified by the consultant photobiologist in the summary letter.

2.1.4 Follow-up

Data from follow-up visits were also collected. Follow-up was usually within six months of phototesting, although longer intervals were also noted. This was considered as being enough time for any photosensitising drug effects to have worn off.

2.1.5 Photoinvestigation

Photoinvestigation was performed over four days, including a variety of different phototesting methods: monochromator testing with narrow-band UVB, UVA, and visible radiation; solar-simulated radiation (SSR), and broadband UVA for provocation testing. In addition, photopatch testing for photocontact allergies to a series of known potential allergens was performed (Kerr et al., 2012).

2.1.5.1 Monochromator phototesting

The patient's upper back was exposed to a dose-series of different wavelengths of UVB, UVA, and visible light to determine the MED. Patients were exposed to different wavelength ; 300, 320, 330, 350, 370, 400, 500, and 600 nm (half-maximum bandwidth 5 nm at 300 nm, 10 nm at 320 and 330 nm; 20 nm at all other wavelengths). Monochromator testing uses a 1KW xenon lamp coupled to a 0.25 mm grating monochromator (Newport Spectra-Physics Ltd, Didcot, UK). Irradiance was measured with a calibrated thermophile (Medical Physics, University Hospital of North Durham, UK) and a digital voltmeter (Medical Physics, Royal Liverpool University Hospital, Liverpool, UK (Moseley et al., 2009).

Monochromator phototesting is a valuable tool to define the responsible action spectrum.The back is observed for 30–60 minutes following exposure for any evidence of an immediate urticarial response. The patient is then re-examined at 24 hours to evaluate the MED response. Finally, a comparison between the patient's MED and normal range was made, Table 2-1 Wavelengths and doses of UVR and visible radiation used in the determination of erythema thresholds, shown in Table 2-1.

Table 2-1 Wavelengths and doses of UVR and visible radiation used in the determination of erythema thresholds in the Photobiology Unit at Salford Royal Hospital

Wavelength nm (± Bandwidth)	**24 h response, J/cm^2**	
	Sensitive range	**Normal range**
300 (5)	0.0018 / 0.0025 / 0.0035 / 0.005 / 0.007 / 0.01	0.014 / 0.02 / 0.028 / 0.04/ 0.08
320 (10)	0.13 / 0.18 / 0.25 / 0.35 / 0.5 / 0.7	1 / 1.4 / 2/ 2.5 / 4
330 (10)	0.31/ 0.44 / 0.63 / 0.9 / 1.3 / 1.8 / 2.5	3.5/ 5 / 7 / 10 / 14
350 (20)	0.63 / 0.9 / 1.3 /1.8 / 2.5 / 3.5 /5 / 7	10 / 14 / 20/ 25 / 40
370 (20)	1.8 / 3.5 / 7 /14	20 / 28 / 57
400 (20)	3.5 / 7 / 14 / 28	40 / 57 / 113
500 (20)	50	
600 (20)	50	

2.1.5.2 Provocation testing

Broadband UVR provocation testing was performed for the assessment and confirmation of the photosensitive conditions. Patients received a single dose of solar-simulated UVR and broadband UVA on 5 x 5 cm areas of the ventral aspect of the forearm on each of three consecutive days. The light sources used to perform the test were a solar simulator (1KW xenon arc lamp with atmospheric attenuation filter; Newport Spectra-Physics Ltd), which was used to deliver a dose of 10 J/cm^2 UVR (290–400 nm) per exposure, and broadband UVA lamps (320–400 nm); Cleo Performance™ bulbs (Phillips Healthcare UK Ltd. Guildford UK) using arm unit to deliver a dose of 15 J/cm^2 per exposure.

2.1.5.3 Patch/photopatch testing

In 2009, the test agents have been updated to involved 24 agents: 19 UVR filters, 5 NSAIDs (Chemotechnique Diagnostics Vellinge, Sweden) (Kerr et al., 2012) and sunscreen products including patients' own. A maximum of 30 agents with the potential to cause a reaction were applied. Day one a duplicate patch was applied to the mid-upper back skin for 24 hours, then one set was covered with a UVR-opaque material and the other set was irradiated with 5 J/cm^2 of broadband UVA (320-400 nm; UVAL 801, Herbert Waldmann GmbH & Co. KG, Villingen-Schwenningen, Germany).

Using the International Contact Dermatitis Research Group (ICDRG) scoring system the skin was assessed pre-irradiation, immediately post-irradiation and 48-72 hours post-irradiation (Kerr et al., 2012). A positive photoallergic response is recorded if a positive reaction to a photoallergen and light is observed (Table 2-2).

Table 2-2 Photopatch testing methodology using the International Contact Dermatitis Research Group (ICDRG) scoring system

Reading	**Day 0 immediately after irradiation**	**Day 1**	**Day 2**	**Day 3**	**Day 4 after irradiation**
	X	X	X	±	±
X, essential readings; ±, desirable readings. ICDRG readings: ?+, doubtful reaction (faint erythema only); +, weak positive reaction (erythema, infiltration, possibly papules); ++, strong positive reaction (erythema, infiltration, papules, vesicles); +++, extreme positive reaction (intense erythema and infiltration and coalescing vesicles or a bulla); IR, irritant reaction; NT, Not tested.					

Adapted from (Bruynzeel et al., 2004)

2.1.6 Dermatology Life Quality Index

The DLQI is a validated questionnaire that has been used for dermatology conditions, although it not specifically designed for photosensitivity conditions(Finlay and Khan, 1994). The Photobiology Unit, Salford Royal NHS Foundation Trust, introduced the routine use of the DLQI questionnaire in 2011. Two questionnaires were completed by patients reflecting on the impact of their condition over both the last week and the last year. The scores for each response were added together to provide DLQI scores out of 30 for the last week and the last year.

2.1.7 Data analysis

Patients' data were collected and summarised in an Excel® spreadsheet. Simple descriptive statistics (mean, standard deviation, percentage) were calculated using Microsoft ® Excel® 2013. To minimise transcription error, data were independently checked by two photobiology doctors, a specialist registrar and a research clinician.

2.2 Project 2: Prevalence and prediction of drug-induced photosensitivity in outpatient clinics (community)

2.2.1 Study design

In this study, a modified version of the PLE prevalence questionnaire previously developed by Dr Tsui Chin Ling in her study of the prevalence and characteristics of PLE was used (Doctor of Medicine thesis degree, University of Manchester 2008). This questionnaire was developed with the expert input of Professor Lesley Rhodes, professor of experimental dermatology at the University of Manchester, and director of the Photobiology Unit at Salford Royal Hospital, Manchester, UK, and Professor Adele Green, professor of epidemiology at the QIMR Berghofer Medical Research Institute Brisbane, Australia. The questionnaire-based survey was performed at Salford Royal Hospital, Manchester from August 2018 to February 2019. Ethical approval was obtained from the West of Scotland Research Ethics Committee (Ref: 18/WS/0130).

The study comprised a questionnaire-based survey of DIP. An anonymous questionnaire was used to ask the participants regarding their current medication and the effect of sun exposure on their skin. Initially, it was expected to collect data from the patient population attending the accident and emergency (A&E) department at Salford Royal NHS Foundation Trust, Manchester, UK. On review by the ethics committee, concerns were raised regarding the potentially vulnerable and distressed state of patients attending A&E departments. In light of these concerns, the target sample population was amended to the outpatient department, specifically the eye and the orthopaedics departments. Before use, the questionnaire was evaluated by a small number of volunteers to ensure it was understandable and easy to complete.

2.2.2 Recruitment process

For a period of six months, from September 2018 to February 2019, patients and their accompanying relatives/carers were approached in the outpatient waiting area at Salford Royal Hospital and invited to participate in the study by completing a face-to-face questionnaire.

- The researcher introduced themselves to the participant, inviting them to take part in the study and taking care to inform them of the following:

  'Before you decide whether to take part, it is important to understand the aims of this study and what it would involve for you. Please take your time to read the following information carefully and ask if anything is not clear or you would like more information'.

- The study was defined as a survey of the prevalence of drug photosensitivity in the community.

- If the participant decided to take part in the study, a participant information sheet and a one-page questionnaire were given by the researcher. It was also emphasised to potential participants that they can withdraw from the study at any time without giving a reason and if they do withdraw from the study, information gathered to that point may still be used in the research, but no additional information will be collected.

- Participants were asked to complete the one-page questionnaire, which asks questions relating to symptoms of DIP and any current medications being taken. To characterise the group of respondents, demographic details, such as age, year of birth, and gender, were also collected.

2.2.3 Sample size

An initial sample of 100 questionnaires was collected from participants, which were used to determine the overall study sample size required to estimate the prevalence of DIP as advised by our collaborating statistician. This estimation was then used to determine the sample size (i.e. number of patients approached) required to estimate prevalence within the community, which was anticipated to be no more than 1000.

2.2.4 Inclusion criteria

Males and females aged 40 years or older with the capacity to understand and complete the questionnaire.

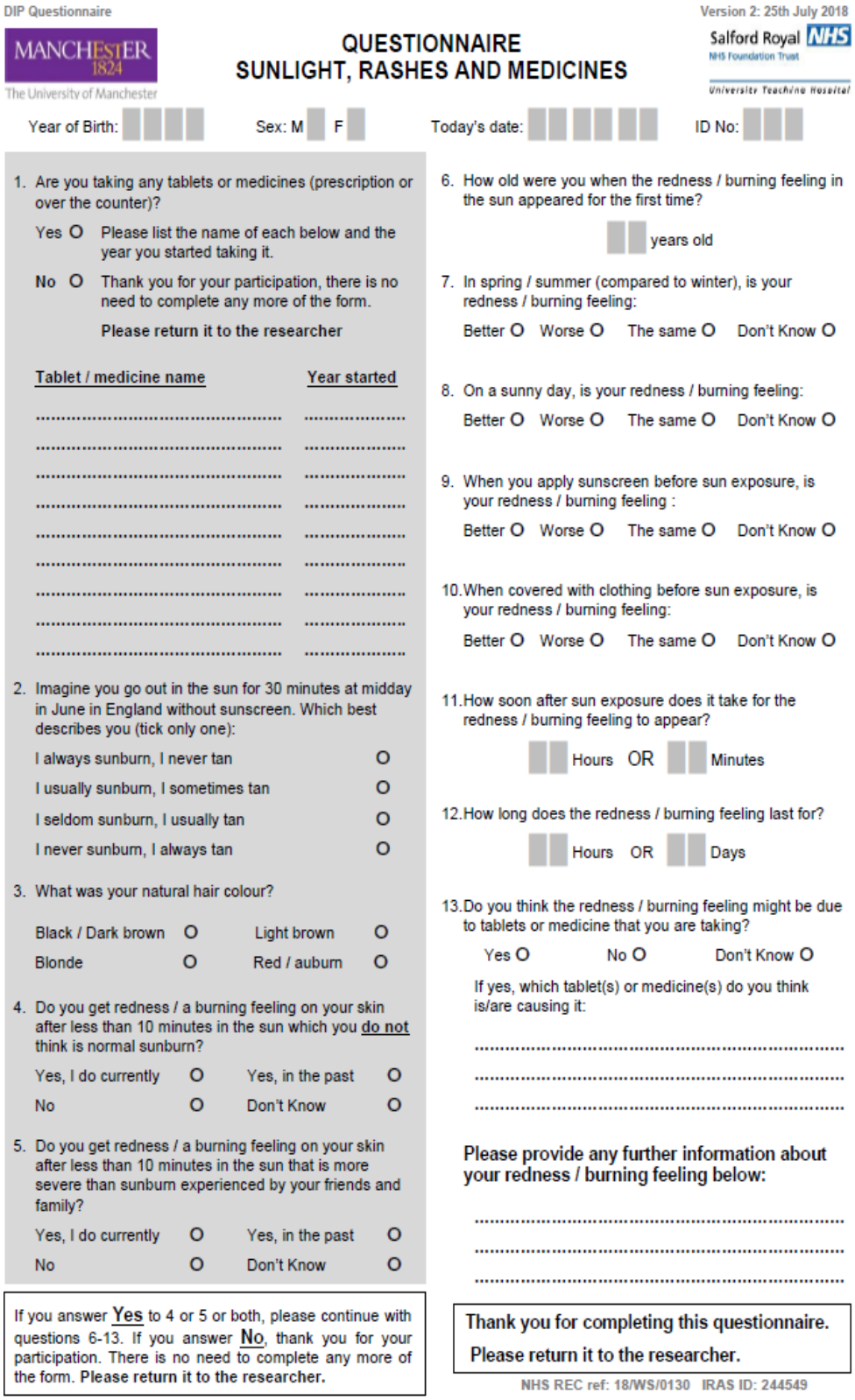
2.2.5 Questionnaire

The questionnaire comprises 13 questions on a single A4 page, figure 2-1. The subject was initially asked to provide basic demographic data (age and gender). The first question was designed to determine if the participant was taking any medications. If the subject answered no (were not taking medication), then they were not asked to complete any further questions.

If the participant answered yes to question 1, they were then asked to list the medications they were taking to identify any potential photosensitising medications. Questions 2 (Imagine you go out in the sun for 30 minutes at midday in June in England without sunscreen, which best describes you?) and Questions 3 (What is/was your natural hair colour?) were used to provide an approximation of the sun-reactive skin type, allowing the identification of phenotypes which might or might not easily develop a sunburn-type response.

Questions 4 (Do you get redness / a burning feeling on your skin after less than 10 minutes in the sun which you do not think is normal sunburn?) and Questions 5 (Do you get redness / a burning feeling on your skin after less than 10 minutes in the sun that is more severe than sunburn experienced by your friends and family?) were key questions in the identification of potential DIP, which is classically described as a red, burning sunburn-type response occurring with minimal light exposure; an exaggerated sunburn response. A positive response to either of these two questions was designated a ‘possible case of DIP’. If the participants answered ‘no’ to both Questions 4 and 5, no further responses were required, and their participation was complete. Having determined that the participant reported an abnormal sunburn-type response (Q4 & Q5) and was taking medication (Q1), Question 6 (How old were you when the redness/burning feeling in the sun appeared for the first time?) was designed to discover whether this abnormal response started before or after they began taking the medication. An abnormal reaction observed after the commencement of medication would support a probable case of DIP, whereas an abnormal reaction before commencement would not.

Questions 7 (In spring/summer, is your redness/burning feeling), Questions 8 (On a sunny day, is your redness/burning feeling), Questions 9 (When you apply sunscreen before sun exposure, is your redness/burning feeling), and Questions 10 (When covered with clothing before sun exposure, is your redness/burning feeling) allow some estimation of the severity of the response and responses can be used to determine whether the 'possible DIP' should be assessed as 'probable DIP'. UVR is present all year round, albeit much less in winter than in summer. If the participants mentioned that the response was the same in winter and summer (Q7), this might suggest that they were very sensitive. Participants describing that they were better in summer than in winter may not have DIP. As with Question 7, Question 8 attempts to identify the degree of response to UVR exposure. Photosensitivity responses are classically worse on days with higher UVR levels ('sunny days'), and participants with potential DIP might be expected to describe a more severe response on a bright day. Questions 9 and 10 attempt to determine how effective protective measures, such as sunscreens and clothing, were. Questions 11 (How soon after sun exposure does it take for the redness / burning feeling to appear?) and Questions 12 (How long does the redness/burning feeling last for?) again provide potential information regarding the type of photosensitivity response. Phototoxic drug reactions typically involve a quicker response and tend to disappear faster while, with other photosensitivity responses and typical 'normal' sunburn, the response may be slower and last longer. Participants may have associated their new medication with an abnormal sunburn-type response, particularly if they had been made aware of potential photosensitivity reactions through the information leaflet provided with their medicine. Question 13 (Do you think the redness/burning feeling might be due to tablets or medicine that you are taking?) was designed to capture this information.



DIP Questionnaire

Version 2: 25th July 2018

The University of Manchester

Salford Royal NHS Foundation Trust

Universities Teaching Hospital

QUESTIONNAIRE
SUNLIGHT, RASHES AND MEDICINES

Year of Birth: ____ Sex: M ☐ F ☐ Today's date: ____ ID No: ____

1. Are you taking any tablets or medicines (prescription or over the counter)?

   Yes O Please list the name of each below and the year you started taking it.

   No O Thank you for your participation, there is no need to complete any more of the form.

   Please return it to the researcher

Tablet / medicine name	Year started
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....
.....	.....

2. Imagine you go out in the sun for 30 minutes at midday in June in England without sunscreen. Which best describes you (tick only one):

   I always sunburn, I never tan O
   I usually sunburn, I sometimes tan O
   I seldom sunburn, I usually tan O
   I never sunburn, I always tan O

3. What was your natural hair colour?

   Black / Dark brown O Light brown O
   Blonde O Red / auburn O

4. Do you get redness / a burning feeling on your skin after less than 10 minutes in the sun which you do not think is normal sunburn?

   Yes, I do currently O Yes, in the past O
   No O Don't Know O

5. Do you get redness / a burning feeling on your skin after less than 10 minutes in the sun that is more severe than sunburn experienced by your friends and family?

   Yes, I do currently O Yes, in the past O
   No O Don't Know O

If you answer Yes to 4 or 5 or both, please continue with questions 6-13. If you answer No, thank you for your participation. There is no need to complete any more of the form. **Please return it to the researcher.**

6. How old were you when the redness / burning feeling in the sun appeared for the first time?

   ☐☐ years old

7. In spring / summer (compared to winter), is your redness / burning feeling:

   Better O Worse O The same O Don't Know O

8. On a sunny day, is your redness / burning feeling:

   Better O Worse O The same O Don't Know O

9. When you apply sunscreen before sun exposure, is your redness / burning feeling :

   Better O Worse O The same O Don't Know O

10. When covered with clothing before sun exposure, is your redness / burning feeling:

    Better O Worse O The same O Don't Know O

11. How soon after sun exposure does it take for the redness / burning feeling to appear?

    ☐☐ Hours OR ☐☐ Minutes

12. How long does the redness / burning feeling last for?

    ☐☐ Hours OR ☐☐ Days

13. Do you think the redness / burning feeling might be due to tablets or medicine that you are taking?

    Yes O No O Don't Know O

    If yes, which tablet(s) or medicine(s) do you think is/are causing it:

    .....
    .....
    .....

Please provide any further information about your redness / burning feeling below:

.....
.....
.....

Thank you for completing this questionnaire.
Please return it to the researcher.

NHS REC ref: 18/WS/0130 IRAS ID: 244549

Figure 2-1 The questionnaire that had been used in the second study

2.2.6 Data analysis plan

A scoring system was developed for participants answers to the questions to facilitate analysis. The first question was the leading question in the questionnaire, which, after excluding the 'no medication' responses, enabled us to distinguish between two participants categories, namely those who 'possibly' have drug photosensitivity versus those who are 'unlikely to' have it. If the participants answer yes to Question 1, that they are taking medication, we would ask them to list their medications. A search was then conducted for each drug, using PubMed® with the search terms 'photosensitivity' 'phototoxicity' and 'photosensit*. Further cross-referencing was done with the reviews by Moore *et al*. (2002), Dufner *et al.* (2006), Drucker and Rosen (2011), Monteiro *et al.* (2016), Blakely *et al.* (2019), and Hofmann *et al*. (2020), (Moore, 2002, Dufner et al., 2006, Drucker and Rosen, 2011, Monteiro et al., 2016a, Blakely et al., 2019, Hofmann et al., 2020). In order to allow groupwise comparisons of the subjects' replies a simple coding system was developed under the guidance of a statistician Dr Elizabeth Marjanovic who is working in School of Biological Sciences division of Musculoskeletal & Dermatological Sciences, University of Manchester. Due to the large number of questionnaires completed and the range of potential replies, a clear and straightforward system to categorise responses was required. The classes were chosen to ensure that all answers were captured, enabling numerical analysis of their responses. The codes used for answers to Questions 2, 3, 4, 5, 7, 8, 9, 10 and 13, are shown in Table 2-3. The data were then entered on an Excel© (Microsoft©) spreadsheet using the code number.

Table 2-3 Scoring system was developed for participants' answers to the questions which were included in the questionnaire to enable data analysis

	Code			
Question	**1**	**2**	**3**	**4**
2	I always sunburn, I never tan	I usually sunburn, I sometimes tan	I seldom sunburn, I usually tan	I never sunburn, I always tan
3	Black / Dark brown	Light brown	Blonde	Red / auburn
4	Yes, I do currently	Yes, in the past	No	Don't Know
5	Yes, I do currently	Yes, in the past	No	Don't Know
7	Better	Worse	The same	Don't Know
8	Better	Worse	The same	Don't Know
9	Better	Worse	The same	Don't Know
10	Better	Worse	The same	Don't Know
13	Yes	No	Don't Know	-

Chapter 3: Prevalence of drug-induced photosensitivity in patients undergoing photoinvestigation

3.1 Introduction

Drug-induced photosensitivity is the reaction between sunlight and a specific chemical agent, leading to adverse cutaneous reactions. The DIP mechanisms, broadly attributable to phototoxicity and photoallergy, occur when photosensitising agents, such as systemic drugs or topically applied chemicals, absorb light at specific wavelengths (Reid, 1996). The spectrum most commonly associated with drug photosensitivity is UVA radiation (320–400 nm). It is important to consider that in some cases, UVB radiation (wavelengths), visible light (wavelengths) or a mixture of different wavebands can induce drug photosensitivity (Diffey and Farr, 1988). Although natural sunlight is involved in DIP, artificial light can also cause significant reactions (Costagliola et al., 2008, Woollons et al., 1997). Artificial UVR sources may include fluorescent lights in offices and UVR lamps used for medical and aesthetic purposes (Fenton et al., 2012). Wide ranges of systemic treatments have been identified as photosensitisin. For example, the antiarrhythmic drug amiodarone; antipsychotic medication, such as chlorpromazine and thioridazine. In addition, antibiotics such as; doxycycline, tetracycline, and nalidixic acid, hydrochlorothiazide in thiazide diuretic; nonsteroidal anti-inflammatory drugs, such as naproxen and piroxicam; and the antifungal drug voriconazole (Drucker and Rosen, 2011, Blakely et al., 2019). Although some progress has been made in developing laboratory-based *in vitro* testing, there are no reliable cutaneous in vivo testing methods (Spielmann et al., 1994, Traynor et al., 2000, Monteiro et al., 2016a). Photosensitivity assessment, carried out at specialist centres, involves exposing the patients to defined spectral ranges of UVR and visible light, then examining the responses for patterns indicative of DIP. Repeat phototesting can be performed after the drug has been stopped for several months, to examine for improvement of photosensitivity. Exploring the link between the culprit drug and phototoxic reaction is an important step for patient management and to prevent drug-induced side effects (Monteiro et al., 2016a). Management of DIP usually by; avoiding exposure to sunlight, applying photoprotective measures, such as sunscreen, protective clothing and stopping the culprit drug if that is possible (Ferguson, 2002).

The prevalence of DIP may be prone to underestimation due to a range of factors. First, lack of compulsory reporting, second, poor awareness of photosensitivity symptoms among both patients and clinicians, finally the complexity of accurately identifying which of a mixture of medication is the actual culprit (Moride et al., 1997, Salathé, 2016, van der Heijden et al., 2002). The photobiological characteristics of DIP associated with different classes of medication are inadequately described, and detailed information regarding the action spectrum rarely provided. In addition, several dermatological conditions have a profound effect on QoL. This study was a retrospective review of patients diagnosed with photosensitivity in the Photobiology Unit (Salford Royal NHS Foundation Trust) between 2000 and 2016. This study aimed to (i) determine the prevalence of DIP among all diagnosed cases of photosensitivity, (ii) determine the most frequent culprit drugs causing DIP and explore for new emerging drugs, (iii) identify the clinical features of patients with DIP, (iv) provide typical phototest data for the most common photosensitising medications, and (v) determine the impact of DIP on QoL.

.

3.2 Results

3.2.1 Patient demographics

A total number of 2,243 of patients underwent investigation in the photobiology unit from 2000–2016. Following the analysis of the patients' data, the prevalence of DIP was noted in 122 patients (5.4%). Of the 122 patients, 64 were female (52.5%). The age range was 11 to 86 years, with a median age of 62 years. An analysis of skin types according to the Fitzpatrick classification revealed the following finding: skin type I (17.2%), II (39.3%), III (26.2%), IV (6.5%), and V (4.1%).

3.2.2 Culprit drugs

The current study found that the commonest drug causing DIP in this patient cohort was quinine, which was reported 14 times (11.5% of all DIP). Another important finding was that DIP due to diuretic represented diuretics (10.7%; thiazide 9.8%) of all cases. Antifungal agents represented 9.8%, and 9.8% of cases were due to PPI. The detailed results of this study shown in Table 3-1.

Table 3-1 Culprit drugs causing DIP in photobiology unit patients 2000–2016
Different drug classes, individual drugs within each class, and the number of patients for which that class/drug was the suspected culprit

Class	**Number of patients (%)**	**Individual drugs within the class (number of patients)**
Antimalarial	15 (12.3%)	Quinine (14) Hydroxychloroquine (1)
Diuretic Thiazide diuretic	13 (10.7%) 12 (9.8%)	Bendroflumethiazide (11) Hydrochlorothiazide (1) Indapamide (thiazide-like diuretic) (1)
Antifungal	12 (9.8%)	Voriconazole (11) Terbinafine (1)
Proton pump inhibitor	12 (9.8%)	Omeprazole (8) Lansoprazole (3) Rabeprazole (1)

Class	Number of patients (%)	Individual drugs within the class (number of patients)
Angiotensin-converting enzyme inhibitors	9 (7.4%)	Enalapril (3) Lisinopril (2) Ramipril (4)
Statins	7 (5.7%)	Simvastatin (5) Atorvastatin (2)
Selective serotonin reuptake inhibitor	6 (4.9%)	Fluoxetine (4) Sertraline (2)
Anti-inflammatory drug	8 (6.6%)	Ibuprofen (2) Naproxen (2) Mesalazine (2) Mefenamic acid (1) Sulfasalazine (1)
Antibiotics	3 (2.5%)	Ciprofloxacin (1) Dapsone (1) Tetracycline (1)
Anti-epileptics	4 (3.3%)	Carbamazepine (2) Phenobarbitone (1) Lamotrigine (1)
Tricyclic antidepressants	4 (3.3%)	Amitriptyline (2) Nortriptyline (2)
Beta-blocker	3 (2.5%)	Atenolol (2) Bisoprolol (1)
Calcium channel blockers	4 (3.3%)	Amlodipine (3) Diltiazem (1)
Immunosuppressants	3 (2.5%)	Azathioprine (3)
Biologics	3 (2.5%)	Etanercept (1) Infliximab (1) Denosumab (1)
Angiotensin-II-receptor antagonists	2 (1.6%)	Candesartan (2)

Class	Number of patients (%)	Individual drugs within the class (number of patients)
Retinoid	2 (1.6%)	Isotretinoin (2)
Other: drugs reported once	13 (10.7%)	Allopurinol, Amiodarone, Bumetanide, Clopidogrel, Colesevelam, Gold injection, Levothyroxine, Metformin, Nicorandil, Parthenolide, Tamoxifen, Tamsulosin, Vitamin B12

3.2.3 Clinical photosensitivity reactions of quinine

DIP due to antimalarials class represented 12.3 %: quinine DIP was reported 14 times (11.5%), and it was the commonest drug reported from this data. While hydroxychloroquine reported once. Further data analysis found that the age range for this drug was 40-85 years, and the median 68 years; ten out of 15 patients were male. Several clinical findings were reported; the most frequently described reactions were the photodistributed lichenoid eruptions and photosensitive eczematous reactions (Table 3.2).

Table 3-2 Clinical photosensitivity reactions of antimalarial

The clinical description of DIP reactions reported from the database in this study where quinine was the most frequent probable culprit drug in the antimalarial group

Clinical response	**Age**	**Sex**	**Drug**
Photodistributed lichenoid drug eruption	75	M	Quinine
Photodistributed lichenoid drug eruption	75	M	Quinine
Photodistributed lichenoid drug eruption	66	F	Quinine
Photodistributed lichenoid drug eruption	63	M	Quinine
Photodistributed lichenoid drug eruption	85	M	Quinine
Photodistributed lichenoid drug eruption	75	M	Quinine
Photosensitive eczematous reaction	62	M	Quinine
Photosensitive eczematous reaction	74	M	Quinine
Photosensitive eczematous reaction with hypopigmentation and hyperpigmentation	62	F	Quinine
Photosensitive eczematous reaction with telangiectasia	40	M	Quinine
Sunburn-like reactions and telangiectasia	51	F	Quinine
Sunburn-like reactions	68	F	Quinine
Sunburn-like reactions	76	M	Quinine
Sunburn-like reactions	63	F	Hydroxychloroquine
Photosensitive eczematous reaction with hypopigmentation and hyperpigmentation	71	M	Quinine and tonic water

3.2.4 Quinine phototesting results

Phototesting revealed positive photoprovocation in response to broadband UVA in 13 of 14 patients tested (93 %) and in 9 of 10 (90%) exposed to SSR. Of the 14 patients who underwent narrow band testing, 11 had reduced MED responses. In 5/11 (45.4%) patients, the lowest MED values were reported in the UVAII range (patient IDs 46, 50, 56, 71 and 108), 2/11 (18.2%) in the UVAI range (patient IDs 92 and 109), with the remaining four (36.4%) patients (patient IDs 69, 84, 114 and 122). MEDs spanned UVAII and UVAI (Table 3-3). In ten out of 15 cases, quinine was identified as the single most likely culprit by the photobiology consultant, and discontinuation was recommended (Table 3-4). Although, it should be noted that most patients were taking a complex mixture of medications, with only one patient taking only quinine. Porphyrin screens were normal in all patients, two patients had raised autoantibodies, and 3/9 patients tested had raised IgE levels. Patch and photopatch testing were negative in all cases. Of the 12 patients where follow-up evaluations had taken place, five had complete resolution of their symptoms, four showed an improvement, symptoms were described as controlled in one case, and a further patient remained symptomatic.

Table 3-3 Quinine phototesting results

Response provoked by broadband UVA, response provoked by solar simulator, abnormal MED and wavelength at which lowest MEDs were reported (nm) for patients with suspected quinine-induced photosensitivity

Patient ID	**Response provoked by broadband UVA**	**Response provoked by solar simulator**	**Abnormal MED**	**Wavelength at which lowest MEDs were reported (nm)**
2	Yes	No	No	-
35	No	Yes	No	-
46	Yes	Yes	Yes	330
50	Yes	Yes	Yes	330
56	Yes	Yes	Yes	330
65	Yes	Yes	Data missing	Data missing
67	*NP	*NP	*NP	*NP
69	Yes	Yes	Yes	320-370
71	Yes	Yes	Yes	330
84	Yes	Yes	Yes	330-370
92	Yes	Yes	Yes	400
108	Yes	*NP	Yes	320
109	Yes	*NP	Yes	350
114	Yes	*NP	Yes	330-350
122	Yes	*NP	Yes	320-350

*Not performed

Table 3-4 Summary of medication taken by patients with suspected quinine-induced photosensitivity

Drugs name at the onset of symptoms, drugs name at the phototesting time, suspected culprit and name of the drug that had been stopped.

Patient IDs	**Drugs being taken at the of onset symptoms**	**Drugs being taken at the time of phototest appointment**	**Suspected culprit**	**Drug stopped**
2	Quinine, Gabapentin, Interferon Beta1-Alpha, Omeprazole, Premarin, Zapain	Quinine, Gabapentin, Docusate, Interferon Beta1-Alpha, Omeprazole, Premarin, Trospium Chloride, Zapain	Quinine Omeprazole	Quinine
35	Quinine, Amlodipine, Aspirin, Atorvastatin Gabapentin, Ibuprofen, Metformin	Quinine, Amlodipine, Aspirin, Atorvastatin, Gabapentin, Ibuprofen, Metformin	Quinine Atorvastatin Ibuprofen	Quinine
46	Quinine, Atorvastatin, Aspirin, Bisoprolol, Fexofenadine, Omeprazole, Ramipril	Atorvastatin, Aspirin, Bisoprolol, Fexofenadine, Omeprazole, Ramipril	Quinine	Quinine
50	Quinine, Atorvastatin, Prochlorperazine	Quinine, Atorvastatin, Prochlorperazine	Quinine	Quinine
56	Quinine, Aspirin, Diltiazem, Ferrous Sulphate, Gliclazide, Isosorbide, Lansoprazole, Loratadine, Metformin, Nicorandil, Simvastatin	Quinine, Aspirin, Diltiazem, Ferrous Sulphate, Gliclazide, Isosorbide, Lansoprazole, Loratadine, Metformin, Nicorandil, Simvastatin	Quinine	Quinine
65	Quinine, Omeprazole, Perindopril, Rosiglitazone, Simvastatin	Quinine, Omeprazole, Rosiglitazone, Simvastatin	Quinine	Quinine
67	Quinine	Quinine, Allopurinol, Doxazosin, Gliclazide, Phyllostine, Ramipril Ranitidine, Simvastatin	Quinine	Quinine

Patient IDs	Drugs being taken at the of onset symptoms	Drugs being taken at the time of phototest appointment	Suspected culprit	Drug stopped
69	Quinine, Amlodipine Clopidogrel, Doxazosin, Indapamide, Senna, Tiotropium, Simvastatin	Quinine, Amlodipine Clopidogrel, Doxazosin, Indapamide, Senna, Tiotropium, Simvastatin	Quinine	Quinine
71	Missing data	Quinine, Ferrous sulphate, Folic acid, Omeprazole, Spironolactone	Quinine	Quinine
84	Ciprofloxacin, Furosemide, Interferon Beta1-Alpha, Ribavirin	Quinine, Citalopram, Hydroxyzine, Spironolactone Zopiclone	Quinine	Quinine
92	Quinine, Loratadine, Premarin, Omeprazole	Loratadine, Omeprazole, Premarin	Premarin or Quinine	Quinine
108	Quinine, Atorvastatin, Tamoxifen, Ramipril	Quinine, Atorvastatin, Tamoxifen, Ramipril	Quinine or Ramipril	Quinine
109	Quinine, Aspirin, Griseofulvin	Quinine, Aspirin, Griseofulvin	Quinine	Quinine
114	Quinine, Amiloride, Bumetanide, Codeine, Gliclazide, Metformin, Paracetamol, Simvastatin, Spironolactone, Sulphate Valsartan	Quinine, Amiloride, Bumetanide, Codeine, Gliclazide, Metformin, Paracetamol, Simvastatin, Spironolactone, Sulphate Valsartan	Quinine Valsartan Bumetanide Amiloride	Quinine Valsartan Bumetanide Amiloride
122	Quinine, Tamsulosin, Theophylline, Hydroxyzine	Quinine, Irbesartan, Tamsulosin, Theophylline Hydroxyzine	Quinine	Quinine

3.2.5 Clinical photosensitivity reactions of thiazide diuretic

A total number of 13 cases (10.7%) reported as DIP were due to diuretic; thiazide was the probable culprit in 12 cases (9.8%), and indapamide reported once. Further analysis showed that the age range was 32–75 years and the median 54 years: ten out of 13 patients were females. Clinically photosensitive eczematous reaction was the most frequently reported reaction, followed by sunburn-like reaction (Table 3-5).

Table 3-5 Clinical photosensitivity reactions of thiazides

The clinical description of DIP reactions reported from the database in this study where thiazides were the probable culprit drug

Clinical reaction	**Age**	**Sex**	**Drug**
Photosensitive eczematous reaction	57	F	Bendroflumethiazide
Photosensitive eczematous reaction	45	M	Bendroflumethiazide
Photosensitive eczematous reaction	44	M	Bendroflumethiazide
Photosensitive eczematous reaction	45	F	Bendroflumethiazide
Photosensitive eczematous reaction	42	F	Bendroflumethiazide
Photosensitive eczematous reaction	32	F	Bendroflumethiazide
Photosensitive eczematous reaction	75	F	Bendroflumethiazide
Photosensitive eczematous reaction	54	F	Bendroflumethiazide
Sunburn-like eruptions	72	F	Bendroflumethiazide
Sunburn-like eruptions	55	F	Bendroflumethiazide
Sunburn-like eruptions	67	M	Bendroflumethiazide
Sunburn-like reaction and telangiectasia	58	F	Indapamide
Sunburn-like reaction	44	F	Hydrochlorothiazide

3.2.6 Thiazide phototesting results

Details of medications taken by patients at the onset of their symptoms and at the time of diagnostic testing are shown in (Table 3-6). Two patients (62 & 68) had stopped taking the suspected culprit by the time of their diagnostic testing appointment (bendroflumethiazide or lisinopril and bendroflumethiazide or irbesartan, respectively). All patients were taking a complex range of medications except for patient 112 (co-amilozide: amiloride & hydrochlorothiazide). Although a further four patients were taking two drugs only (62, 68, 116 & 125), these were drugs associated with photosensitivity in two cases (68 & 125). Patients 62 & 116 were taking drugs additional to bendroflumethiazide that were not reported to be associated with photosensitivity.

Table 3-6 Summary of medication taken by patients with suspected thiazide-induced photosensitivity.

Drugs name at the onset of symptoms, drugs name at the phototesting time, suspected culprit and name of the drug that had been stopped

Patient ID	**Drugs being taken at the onset of symptoms**	**Drugs being taken at the time of phototest appointment**	**Suspected culprit**
22	Bendroflumethiazide, Diltiazem	Indapamide, Doxazosin, Fexofenadine	Bendroflumethiazide
45	Indapamide. Betahistine Clopidogrel, Fenofibrate, Irbesartan, Lansoprazole, Trimethoprim	Indapamide, Betahistine, Buscopan, Clopidogrel, Fenofibrate, Irbesartan, Lansoprazole	Clopidogrel, Fenofibrate, Indapamide, Irbesarta, Lansoprazole
57	Bendroflumethiazide Bisoprolol, Isosorbide, Levothyroxine, Mebeverine, Mononitrate, Omeprazole, Senna, Zapain	Bendroflumethiazide, Isosorbide, Mononitrate, Bisoprolol, Zapain, Levothyroxine, Mebeverine, Omeprazole, Senna	Bendroflumethiazide
61	Benzofluazide, Aspirin, Atenolol Irbesartan, Naproxen	Benzofluazide, Atenolol, Irbesartan, Fluoxetine, NSAIDS, Zapain	Thiazide, Fluoxetine. NSAID

Patient ID	Drugs being taken at the onset of symptoms	Drugs being taken at the time of phototest appointment	Suspected culprit
62	Benzofluazide, Lisinopril	Bisoprolol, Losartan	Benzofluazide Lisinopril
68	Bendroflumethiazide, Irbesartan	Mirtazapine, Pravastatin, Oxycodone	Bendroflumethiazide Irbesartan
76	Bendroflumethiazide, Alendronic acid, Omeprazole, Losartan	Bendroflumethiazide, Alendronic acid, Omeprazole, Losartan	Bendroflumethiazide
81	Bendroflumethiazide, Amlodipine	Bendroflumethiazide Amlodipine	Bendroflumethiazide
104	Bendroflumethiazide Amitriptyline, Aspirin, Atenolol, Venlafaxine	Bendroflumethiazide, Amitriptyline, Aspirin, Atenolol, Venlafaxine	Bendroflumethiazide
105	Benzofluazide, Fluoxetine, Frusemide, Nifedipine, Topiramate	Benzofluazide, Fluoxetine Frusemide, Nifedipine, Topiramate	Benzofluazide
107	Benzofluazide, Amitriptyline Doxazosin, Losartan	Benzofluazide, Amitriptyline, Doxazosin	Benzofluazide Amitriptyline
112	Co-amilozide (amiloride and hydrochlorothiazide)	Co-amilozide (amiloride and hydrochlorothiazide)	Hydrochlorothiazide
116	Benzofluazide, Co-codamol	Benzofluazide, Co-codamol	Benzofluazide
125	Hydrochlorothiazide, Enalapril	Aspirin, Cyclosporin, Ranitidine, Prednisolone Simvastatin	Hydrochlorothiazide Enalapril

On phototesting, a positive response to broadband UVA provocation was observed in 12 (92.3%) patients. The response was described as mild in five cases (patient IDs 22, 45,57,68 & 104), mild to moderate in one (patient 107), moderate in two cases (patients 61 & 112), and moderate to severe in another case (patient116) (Table 3.7). An eczematous response was noted in two cases (patients 81 & 105). One response had been described by the clinical team as 'definite' in the results proforma. Eight patients underwent SSR provocation testing, with a reaction observed in seven (87.5%) patients. Of these seven positive cases, two responses were mild (patients 22, 62), two were moderate (patients 45 & 57), one was moderate to severe (patient 61), one 'definite' (patient 76), and one eczematous (patient 81); narrowband monochromator testing showed reduced erythemal threshold in only three cases (patients 57, 81 &116) centred around the UVA wavelengths. In 8/14 cases, the thiazide was identified as the single most likely culprit by the photobiology consultant. Of the six patients where follow-up information was available, four were improving (patients 57, 62, 68 & 81), one' symptoms had resolved (patient 22), and one remained symptomatic at 20 months (patient 61). IgE results were available in eight cases, of which four were raised, (two of these patients were known to be atopic). Porphyrin screens and autoantibody screens were negative in all cases. A further two patients had incidental findings of positive patch test responses to benzophenone three and octyl methoxycinnamate (patient 81) and their own sunscreen (patient 116).

Table 3-7 Thiazide phototesting results

Response provoked by broadband UVA, response provoked by solar simulator, abnormal MED and wavelength at which lowest MEDs were reported (nm) for patients with suspected thiazide -induced photosensitivity

Patient ID	**Response provoked by broadband UVA**	**Response provoked by solar simulator**	**Abnormal MED**	**The wavelength at which lowest MEDs were reported (nm)**
22	Yes	Yes	No	-
45	Yes	Yes	No	-
57	Yes	Yes	Yes	330–350
61	Yes	Yes	No	-
62	No	Yes	No	-
68	Yes	No	No	-
76	Yes	Yes	No	-
81	Yes	Yes	Yes	320–400
104	Yes	*NP	No	-
105	Yes	NP	No	-
107	Yes	NP	No	-
110	No	NP	No	-
112	Yes	Np	No	-
116	Yes	Np	Yes	370
125	No	NP	No	-

*Not performed

3.2.7 Clinical photosensitivity reactions of antifungals

A total of 11 cases were reported as DIP due to antifungal agents. Voriconazole was the probable culprit in ten cases and terbinafine was observed in one case. The age range was 59–80 years and the median 64 years. Five out of 11 patients were female. Clinically sunburn-like eruptions cheilitis were the commonest observed drug reactions (Table 3-8).

Table 3-8 Clinical photosensitivity reactions of antifungals

The clinical description of DIP reactions reported from the database in this study where antifungals were the probable culprit drug

Clinical reactions	**Age**	**Sex**	**Drug**
Sunburn-like eruptions	61	M	Voriconazole
Sunburn-like eruptions	57	M	Voriconazole
Sunburn-like eruptions	72	F	Voriconazole
Sunburn-like eruptions	68	M	Voriconazole
Sunburn-like eruptions	67	M	Voriconazole
Sunburn-like eruptions and cheilitis	64	F	Voriconazole
Sunburn-like eruptions and cheilitis	66	M	Voriconazole
Sunburn-like eruptions and cheilitis	80	M	Voriconazole
Sunburn-like eruptions and cheilitis	59	F	Voriconazole
Sunburn-like eruptions and cheilitis	69	F	Voriconazole
Sunburn-like eruptions and multiple lentigines (pigmented lesions)	62	M	Voriconazole
Sunburn-like eruptions and multiple lentigines (pigmented lesions)	59	F	Terbinafine

3.2.8 Antifungal phototesting results

The range of medications taken by the 11 patients diagnosed with DIP linked to antifungal medications shown in (Table 3-9). In all cases, the photobiology consultant identified the antifungal drug as the single most likely causative agent, although, as with other drug-induced photosensitive patients, the majority were taking a complex range of drugs. Eleven of the 12 cases were linked to voriconazole and have been reported in part of a series published by the photobiology unit in 2013 (Haylett et al. 2013). The remaining single antifungal-associated reaction was linked to terbinafine (patient 100). Table 3-10 summarises the results of phototesting; this revealed a positive provocation response to broadband UVA in 10 out of 12 cases (83.3%) with a negative response observed in patients taking voriconazole (patient 82) and terbinafine (patient 100). The response was described as mild erythema in the majority of cases with a moderate response reported in only a single patient (patient 70). SSR provocation testing was only performed in the 11 patients taking voriconazole, with results mirroring those seen with broadband UVA (i.e., negative in patient 82), albeit a slightly greater number of responses described as moderate (patients 49, 70 & 80). Five patients had reduced narrow band erythemal thresholds (patients 49, 54, 58, 70 & 80), with 370 nm being the most frequent provoking wavelength. All narrowband responses were seen in patients taking voriconazole, and no abnormal response was seen in the patient taking terbinafine. Follow-up details were unavailable for the voriconazole patients as all had been discharged back to the referring respiratory consultant. The symptoms of the patient with terbinafine-associated photosensitivity were resolving.

Table 3-9 Summary of medication taken by patients with suspected antifungal-induced photosensitivity

Drugs name at the onset the of symptoms, drugs name at the phototesting time, suspected culprit and name of the drug that had been stopped

Patient ID	Drugs being taken at the onset of symptoms	Drugs being taken at the time of phototest appointment	Suspected culprit
16	Voriconazole, Prednisolone, Lactulose, Senna	Voriconazole, Prednisolone, Senna	Voriconazole
49	Voriconazole, Aspirin, Zapain Ramipril, Pravastatin, Naproxen	Voriconazole, Aspirin, Ramipril, Pravastatin, Zapain	Voriconazole
54	Voriconazole, Levothyroxine, Simvastatin	Voriconazole, Levothyroxine, Simvastatin	Voriconazole
58	Voriconazole, Carbocysteine, Metformin, Fludrocortisone, Lisinopril, Calcichew	Voriconazole, Carbocysteine, Metformin, Fludrocortisone, Lisinopril, Calcichew, Doxycycline	Voriconazole
70	Voriconazole, Amitriptyline, Nifedipine, Lansoprazole	Voriconazole, Ciprofloxacin, Spironolactone, Amitriptyline, Nifedipine, Co-codamol, Lansoprazole, Warfarin, Hydroxychloroquine, Levothyroxine	Voriconazole
74	Voriconazole, Flecainide, Omeprazole	Voriconazole, Flecainide, Citalopram, Aspirin, Codeine, Azithromycin, Omeprazole	Voriconazole
78	Voriconazole, Aspirin, Atenolol, Pravastatin.	Voriconazole, Aspirin, Atenolol, Pravastatin	Voriconazole
80	Voriconazole, Ciprofloxacin, Fluticasone	Voriconazole, Ciprofloxacin, Fluticasone	Voriconazole
82	Ventolin, Zopiclone, Uniphyllin continus Quinine, Omeprazole, Candesartan, Bendrofluazide, Itraconazole	Voriconazole, Zopiclone, Uniphyllin continus, Quinine, Omeprazole, Candesartan, Bendrofluazide	Voriconazole
85	Voriconazole, Ramipril Citalopram, Carbocisteine	Voriconazole, Carbocisteine, Ramipril, Citalopram	Voriconazole
86	Voriconazole, prednisolone	Voriconazole	Voriconazole
100	Terbinafine		Terbinafine

Table 3-10 Antifungal phototesting results

Response provoked by broadband UVA, response provoked by solar simulator, abnormal MED and wavelength at which lowest MEDs were reported (nm) for patients with suspected antifungal -induced photosensitivity

Patient ID	**Response provoked by broadband UVA**	**Response provoked by solar simulator**	**Abnormal MED**	**The wavelength at which lowest MEDs were reported (nm)**
16	Yes	Yes	No	-
49	Yes	Yes	Yes	370
54	Yes	Yes	Yes	370
58	Yes	Yes	Yes	370
70	Yes	Yes	Yes	320–350
74	Yes	Yes	No	-
78	Yes	Yes	No	-
80	Yes	Yes	Yes	370
82	No	No	No	-
85	Yes	Yes	No	-
86	Yes	Yes	No	-
100	No	*NP	No	-

*Not performed

3.2.9 Clinical photosensitivity reactions to proton pump inhibitor

A notable finding in this data was that PPI was a probable culprit in 12 cases: in eight cases omeprazole, three cases lansoprazole, and one case rabeprazole. Data analysis showed that nine patients were male. The median age was 59 years, while the age range was 37–75 years. Sunburn-like reactions and photosensitive eczematous reaction were the most recognisable reactions (Table 3-11).

Table 3-11 Clinical photosensitivity reactions of proton pump inhibitor

The clinical description of DIP reactions reported from the database in this study where proton pump inhibitors were the probable culprit drugs

Clinical reaction	**Age**	**Sex**	**Drug**
Sunburn-like reactions	61	M	Omeprazole
Sunburn-like reactions	65	M	Omeprazole
Sunburn-like reactions	40	F	Omeprazole
Sunburn-like reactions	63	F	Omeprazole
Sunburn-like reactions	59	M	Omeprazole
Sunburn-like reactions	48	F	Omeprazole
Photosensitive eczematous reaction	62	M	Omeprazole
Photosensitive eczematous reaction	72	M	Omeprazole
Photosensitive eczematous reaction	45	M	Lansoprazole
Photosensitive eczematous reaction	61	M	Lansoprazole
Sunburn-like reactions	41	M	Lansoprazole
PLE exacerbated reaction	37	M	Rabeprazole

3.2.10 Proton pump inhibitor phototesting results

Table 3-12 details the range of medications taken by the 12 patients in whom PPIs were identified as a likely cause of the photosensitivity. The majority of patients were taking a complex range of medications, except for two patients, 37 & 79, who were taking omeprazole and rabeprazole, respectively. In six cases (patients 17, 21, 27, 37, 79 & 106), a PPI was identified as the single most likely culprit. Phototesting showed a positive response to broadband UVA and SSR in all cases tested. Reduced narrow band MED thresholds were observed in only three individuals (patients 21, 94 & 106), at wavelengths in the UVA II range. (320–330 nm) (Table 3-13). Two of the 11 patients tested had abnormal autoantibody results (patients 33 & 94), with raised DNA 250 (patient 33) and ANA positive 1:1000 speckled (patient 94). Interestingly, patient 94 was also reported to have a weakly positive porphyrin screen response at 622 nm, although a diagnosis of porphyria appears to have been discounted by the photobiology consultant. IgE levels were available for eight patients, out of whom two had raised levels (patients 33 & 63). A co-incidental finding of a contact allergy to the UVR filter methylene bis-benzotriazolyl tetramethyl butylphenol (Tinasorb M) was also reported (patient 21). Out of six patients whose follow-up details were available, two were unable/unwilling to stop their use of PPIs, two remained symptomatic, one was improving, and symptoms had resolved in one case.

Table 3-12 Summary of medication taken by patients with suspected proton pump inhibitor-induced photosensitivity

Drugs name at the onset the of symptoms, drugs name at the phototesting time, suspected culprit and name of the drug that had been stopped

Patient ID	**Drugs being taken at the onset of symptoms**	**Drugs being taken at the time of phototest appointment**	**Suspected culprit**
17	Omeprazole, Ibuprofen	Omeprazole	Omeprazole
18	Lansoprazole, Mesalazine	Lansoprazole, Mesalazine	Lansoprazole or Mesalazine
21	Omeprazole, Felodipine	Ramipril, Levothyroxine, Aspirin	Omeprazole
23	Lansoprazole, Felodipine, Aspirin, Irbesartan, Atorvastatin, Fluoxetine	Lansoprazole, Aspirin, Felodipine, Irbesartan, Atorvastatin, Fluoxetine	Lansoprazole or Aspirin
27	Omeprazole, Fexofenadine	Fexofenadine, Omeprazole	Omeprazole
33	Omeprazole, Doxycycline Metformin, Glibenclamide, Pioglitazone, Bisoprolol, Lisinopril, Aspirin, Simvastatin, Isosorbide, Nicorandil	Omeprazole, Doxycycline, Metformin, Glibenclamide, Pioglitazone, Bisoprolol Lisinopril, Aspirin, Simvastatin, Isosorbide, Nicorandil	Omeprazole Nicorandil Isosorbide
37	Omeprazole	Omeprazole	Omeprazole
63	Omeprazole, Aspirin, Atorvastatin, Metformin, Procoralan, Venlafaxine	Omeprazole, Aspirin, Atorvastatin, Duloxetine, Metformin, Nifedipine, Procoralan, Promazine, Liraglutide, Clopidogrel	Atorvastatin or Omeprazole
79	Rabeprazole	Rabeprazole	Rabeprazole
94	Omeprazole, Ciclosporin, Enalapril, Pravastatin, Furosemide	Omeprazole, Ciclosporin, Doxazosin, Enalapril, Pravastatin, Furosemide, Mycophenolate, Amlodipine	Omeprazole Enalapril Frusemide or Amlodipine
106	Omeprazole, Bendrofluazide, Candesartan, Doxazosin	Omeprazole, Candesartan, Doxazosin	Omeprazole

Table 3-13 Proton pump inhibitor phototesting results

Response provoked by broadband UVA, response provoked by solar simulator, abnormal MED and wavelength at which lowest MEDs were reported (nm) for patients with suspected proton pump inhibitor induced photosensitivity

Patient ID	**Response provoked by broadband UVA**	**Response provoked by solar simulator**	**Abnormal MED**	**The wavelength at which lowest MEDs were reported (nm)**
17	Yes	Yes	No	-
18	Yes	Yes	No	-
21	Yes	Yes	Yes	320
23	Yes	Yes	No	-
27	Yes	Yes	No	-
33	Yes	Yes	No	-
37	Yes	Yes	No	-
63	Yes	Yes	No	-
79	Yes	Yes	No	-
94	Yes	Yes	Yes	330
106	Yes	*NP	Yes	320

*Not performed

3.2.11 Dermatology Life Quality Index findings

The one-page validated DLQI questionnaire was used to assess the effect of DIP on patients' QoL, although it is not specific for photosensitivity conditions. The DLQI questionnaire had been routinely used in photoinvestigation since 2011. Hence, the DLQI questionnaire had been completed by 54 patients (for the past week) and 58 patients (for the last year). Summary data shown in Table 3-14. DLQI for the past week was reported as follows: the effect on the QoL was moderately large impaired in 13/54 patients (24%), very large impaired in 12/54 patients (22%), and extremely large impaired in two patients (2/54; 3.7%). The DLQI scores for the past year showed greater impacts. The effect on the QoL was found to be moderately large impaired in 23/58 patients (40%) and very large impaired in 19/58 (32%), while 11/58 (19%) indicated an extremely large impact on the QoL.

Table 3-14 DLQI data

The number of patients performed DLQI (past week/past year), the median of DLQI score, percentage of patients with DLQI >10 and patient age (mean and range)

DLQI	**Number of patients who completed the questionnaire**	**Median of DLQI score** (Range)	**Percentage of patients with DLQI >10**	**Age (years)**
DLQI for the past week	54	6 (0-29)	59%	Mean: 59.5 Range; 11–86
DLQI for the past year	58	11 (2-27)	65%	Mean: 58.9 Range: 11–86

3.3 Discussion

This study found that the prevalence of DIP was 5.4% in patients attending for photoinvestigation. In this study, female patients represented 52.5%, with ages ranging from 11–86 years (median 62 years). Further data analysis showed that sun-reactive skin types were as follows: I (17.2%), II (39.3%), III (26.2%), IV (6.5%), and V (4.1%). Closer inspection of culprit drugs revealed that four drug categories were the most common causes of DIP and were responsible for 44% of cases. Quinine-induced photosensitivity represented 11.5% and diuretic represented 10.7% (thiazide 9.8%). An important finding was that DIP due to antifungals represented 9.8%, and the most interesting finding was that PPIs represented 9.8% of DIP cases.

The DLQI questionnaire was used to evaluate the impact of DIP on QoL; patients were asked to reflect on the impact of their condition over the past week and past year. The DLQI for the past week was completed by 54 patients and showed that the effect of DIP on QoL was moderately large impaired in 24% of responders, very largely impaired in 22%, and extremely large impairment in 3.7%. The DLQI for the past year was completed by 58 patients and showed that 40% believed that their condition moderately large impaired their QoL; very large impairment was reported in 32% of patients, and 19% noted an extremely large impairment on their QoL.

3.3.1 Reporting of drug photosensitivity

Estimation of the prevalence of DIP is fundamentally vital for several reasons, including the development of an appropriate patient-focused healthcare plan, improving the clinician’s knowledge of the condition leading to improvement in disease diagnosis (potentially leading to a resolution of the patient's photosensitivity), and, finally, identifying the burden of the disease on the community (Ward, 2013). Prevalence estimates from this study may well be an underestimate due to the dependence of the estimate on the numbers of patients being referred. Only a few photobiology test centres exist in the UK. Referral relies on GPs recognising a potential photosensitivity disorder and being aware of the availability of testing facilities. Furthermore, patients often have to be prepared to travel large distances, and the impact of the latter can be seen in the relatively high numbers who did not attend their follow-up appointments.

3.3.2 Quinine

Quinine was reported to be the culprit drug in 14 cases (11.5%) in this data set. Quinine has been used to treat malaria and muscle cramps, and is also added to soft drinks, such as tonic water (El-Tawil et al., 2015, Shanks, 2016). It has been reported that quinine-induced photodamage to cellular DNA is through the production of singlet oxygen and/or free radicals (Moore and Hemmens, 1982, Spikes, 1989). It has been reported to induce both photoallergic and phototoxic reactions (Ferguson et al., 1987). The action spectrum of quinine-induced photosensitivity patients has been reported to lie in the UVA range (Wolf et al., 1987).

In a search of the literature for quinine-induced photosensitivity, several reports were identified (Appendix 1). Comparison with published case reports revealed almost similar age distribution, reported data from this study: median 68 years, range (40–85 years) *versus* literature data set: median 62 years, range (38–84 years). The data presented here show a higher male: male ratio than in the literature (10 M: 5 F *versus* 16 F: 10 M, respectively), but this may simply reflect differences in prescribing practices regionally and internationally.

Quinine can induce different photo-adverse reactions: sunburn-like reactions, including photodistributed erythema and oedema (Ferguson et al., 1987); altered skin pigmentation (Wahlberg and Boman, 1981); and eczematous eruptions (Delmas and Plantin, 1995a, Ljunggren and Sjövall, 1986, Liunggren et al., 1992). Lichenoid reaction and photo-onycholysis have also been reported (Ferguson et al., 1987, Dawson, 1986, Thomas and Munro, 1986, Tan et al., 1989). In comparison to these findings, this study revealed that the most common reactions were photodistributed lichenoid drug eruptions and photosensitive eczematous reactions.

The results demonstrate sensitivity to UVA in patients, with the majority responding to broadband UVA and SSR testing. Narrowband testing identified UVAII as key wavelengths in 45% of patients. Quinine has an absorption range of between 300 and 350 nm, peaking at 330 nm in water or phosphate-buffered saline (Aloisi et al., 2007). In a biological environment, this might be predicted to undergo a redshift to longer wavelengths, and *in vivo* case reports of narrowband testing have shown reduced thresholds at a range of wavelengths. Ferguson *et al.* (1987) reported four cases with thresholds reduced at 335–365 nm, 305–430 nm, and 305–365 nm (Ferguson et al., 1987).

Similarly, Diffey *et al.* (1988) reported three cases with reduced thresholds at 330–370 nm, 320–370 nm, and 320–370 nm (Diffey et al., 1988).

3.3.3 Diuretics

Photosensitivity reactions to diuretics were observed in 13 cases in this study (10.7%), where thiazide diuretics were the most reported drug 12 cases (9.8%). Diuretics are a group of medications that are often used to treat hypertension; thiazides are the most common drug in this group. Thiazide photosensitivity reactions have been reported since shortly after the drug was introduced to the market in the 1950s and had been reported as one of the most frequent causes of photosensitivity reactions (Selvaag and Thune, 1997, Harber et al., 1959a). The skin reaction can present clinically as severe sunburn reactions or lichenoid skin lesions. In addition, chronic eczematous photosensitivity can persist for months to years, even after the withdrawal of the causative drug (Robinson et al., 1985; Addo et al., 1987, Johnston and Coulson, 2002). The action spectrum responsible for inducing DIP by hydrochlorothiazide appears to be wavelengths in the UVA range (Torinuki, 1980).

In a search of the literature, several cases of thiazide-induced photosensitivity were found; these cases are summarised (Appendix 2). The median age of patients at symptom onset was lower in our patients than in the case reports reviewed (median 68: range 42–77 years versus median 54: range 32–75 years in our data); however, this may, again, simply reflect prescribing and referral patterns.

The data in this study observed DIP in ten females compare with 64 cases from the literature (34 females and 29 males). However, the prevalence of thiazide-induced photosensitivity is rarely described in the literature, with most of the reports presented as case reports (Gómez-Bernal et al., 2014). Clinical observation in this study revealed that photosensitive eczematous reaction and sunburn-like eruptions were the most common photosensitive skin reactions. Some studies have reported that hydrochlorothiazide can cause photosensitivity with features of SLCE; however, this was not observed in any patients in this study (Darken and McBurney, 1988, Parodi et al., 1989, Brown and Deng, 1995, Srivastava et al., 2003).

Of the patients taking bendroflumethiazide, the majority (n = 8) showed normal erythemal thresholds on narrowband testing, and, where the thresholds were reduced (n = 3), UVA was the key wavelengths. Broadband UVA testing similarly provoked abnormal responses in the majority of those tested (n = 10). Although thiazide diuretics are associated with photosensitivity, clinical studies or case reports are rare, particularly concerning bendroflumethiazide, which the majority (11) of our patients were taking.

Addo *et al.* (1987) report UVA sensitivity in a patient taking bendroflumethiazide (Neo-naclex) in addition to the thiazide diuretic Moduretic (amiloride and hydrochlorothiazide), cyclopenthiazide, and the antidepressant amitriptyline. In a second case, Addo *et al.*(1987) reported both UVB and UVA sensitivity in a patient taking bendroflumethiazide (Neo-naclex) in addition to captopril, diazepam, and methyldopa (Aldomet) (Addo et al., 1987).

The largest study, by Diffey *et al*. (1989), tested 13 patients for sensitivity to narrowband UVB and UVA before and after a 2-week course of bendroflumethiazide (Diffey and Langtry, 1989). No abnormal MED results were reported, although a relative reduction in MED was observed. These results suggest a sensitivity to broadband UVA, with abnormal responses to narrowband testing being more unusual. Interpretation was complicated by the complex range of medicines being taken. Two patients who were taking hydrochlorothiazide did not show reduced narrow band thresholds, and only one was provoked by broadband UVA, although it should be noted the latter was a rare case of a patient taking only a single drug. Hydrochlorothiazide has been associated with UVA sensitivity in two-single case studies (Torinuki, 1980; Harber et al. 1959). Addo *et al*. (1987) also reported a case series of 18 patients taking Moduretic (hydrochlorothiazide and amiloride) reporting abnormal (Addo et al., 1987).

Narrowband testing in 13 of the 15 tested. Diffey *et al*. (1989) detailed nine patients who underwent narrowband testing, reporting normal MEDs in all cases (Diffey and Langtry, 1989). A single case of indapamide-associated photosensitivity was seen, which, similar to bendroflumethiazide and hydrochlorothiazide was associated with broadband UVA sensitivity. Indapamide-induced photosensitivity has only been reported as a single case study of light-induced onycholysis (Rutherford & Sinclair 2007).

3.3.4 Voriconazole

Reactions were observed 11 times in our data (9.8%). Voriconazole is a second-generation triazole antifungal drug that is used to treat various fungal infections, such as invasive aspergillosis, oesophageal candidiasis, and serious candida infections (Health, 2017, Patel et al., 2019). Photosensitivity is the second most commonly reported side-effect for voriconazole (Boyd et al., 2004). The action spectrum responsible for inducing photosensitivity reaction is UVA (Haylett, Felton et al. 2013). A comparison of patients' gender in this study to the literature showed that these were similar, namely 7 M: 5 F versus 64 M: 54 F, respectively. The cases seen in Manchester were referred from the National Aspergillosis Centre, which is based in Manchester.

A comparison of age groups with the published case reports reveals different age distributions (range: 4–86 versus range 59–80 years in our data), and it is difficult to calculate the age median from the reported cases in the literature due to lack of information in some of these studies.

Clinically, sunburn-like eruptions and cheilitis were the most commonly reported cutaneous reaction in our patients, while the clinical images from the literature showed several phototoxicity reactions, such as photodistributed erythema, pseudoporphyria, and actinic cheilitis (summarised in Appendix 3) (Denning and Griffiths, 2001, Tolland et al., 2007). In addition, severe adverse skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported (Curigliano et al., 2006, Saravolatz et al., 2003). Furthermore, it has been reported that immunocompromised patients have an increased tendency to develop squamous cell carcinomas (SCC) and melanoma in situ (Cowen, Nguyen et al., 2010; Miller, Cowen et al., 2010). Itraconazole is another of the triazole group that has been linked to photosensitivity (Alvarez-Fernández, Castaño-Suárez et al., 2000). Similarly, ketoconazole, of the imidazole group of antifungals, has been associated with phototoxic dermatitis (Mohamed, 1988).

Photosensitivity was confirmed in the majority of patients in this study with the use of broadband UVA or SSR radiation. There have been several reports of photosensitivity associated with voriconazole (Abdel-Haq et al., 2014, Bernhard et al., 2012), although the underlying mechanism is still unknown. It has been suggested that a metabolite of voriconazole may be responsible (Epaulard et al., 2011). Alternatively, increased retinol levels have also been suggested as a possible cause (Denning and Griffiths, 2001).

The single patient diagnosed with terbinafine-associated photosensitivity did not show any positive responses to testing, with normal ANA results also reported. The majority of reports of terbinafine-associated photosensitivity describe drug-induced SCLE (Fabbri et al., 2003, Ramachandran et al., 2017).

However, Kuo *et al*. (2014) described a case of suspected terbinafine-induced solar urticaria with sensitivity to UVB (Kuo and Sivamani, 2014). Spiewak *et al*. (2010) reported a case of terbinafine-associated photoallergy with a positive photocontact response (UVA) two months after the patient had stopped their course of terbinafine (Spiewak, 2010). The patient did not show any positive responses to testing, but this was reported as likely due to terbinafine treatment being stopped before the patient could be tested.

3.3.5 Proton pump inhibitors

This retrospective study revealed that PPIs were reported as the likely culprit drug in 12 cases (9.8%). PPIs are a group of medications consisting of omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole, and tenatoprazole. Omeprazole, introduced in the year 2002, was the first commercially available PPI. This medication can inhibit the proton pump function (H+/K+ ATPase) and works as a gastric acid suppressor (Richardson, Hawkey et al. 1998). A search of the literature revealed that SCLE has been reported as an adverse drug reaction of PPI (Appendix 4). SCLE, a subtype of cutaneous lupus erythematosus with limited systemic involvement, clinically manifests as erythematous scaly plaques or psoriasiform papulosquamous lesions (Lowe et al., 2011). Photoallergic dermatitis with multiple pruritic erythematous skin lesions in a female patient after treatment with 40 mg of esomeprazole has also been reported (Shukla, Mahapatra et al. 2010). In contrast, the data from our study reported that sunburn-like reactions and photosensitive eczematous reaction were the most common adverse drug reactions.

In comparison, the median age of symptom onset reported in the literature was 63 years versus 59 years in this study. The age range was 37–65 years in this data versus 30–85 in the literature. We observed DIP in eight males and four females versus 16 females and three males in literature. However, this may simply reflect the relatively low number of patients in both this and previous studies.

Broadband UVA and SSR successfully provoked a response in all the patients diagnosed with PPI-associated photosensitivity. PPIs have been principally associated with case reports of drug-induced SCLE (Almebaydh, 2013; Bracke, 2004; Dam, 2007; Messeguer, 2011; and Panting 2009) or Discoid lupus erythematosus (DLE) (Corriea 2001), with photosensitivity specifically mentioned in only 15 of the 32 drug-induced SCLE/DLE cases described. The cases of PPI-induced photosensitivity described here were not associated with SCLE-like symptoms, rather a frank photosensitivity response. A search of PubMed® revealed only a single case of PPIs associated with photosensitivity without the development of lupus; a report of esomeprazole associated with photosensitivity (Shukla et al., 2010).

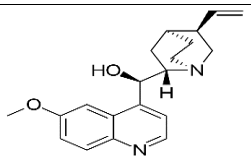
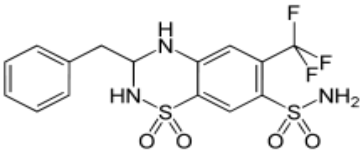
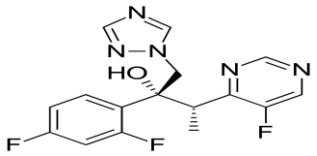
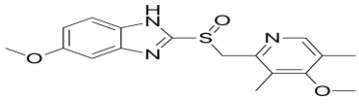
The majority (8) of the 12 patients detailed here were taking omeprazole, three were taking lansoprazole, and a single patient was taking rabeprazole. No cases of photosensitivity associated with omeprazole or lansoprazole could be found in the literature; the manufacturer is describing symptoms of photosensitivity as rare (between 1:10,000 and 1:1000). It is interesting to note that in the case of rabeprazole, the manufacturer does not list photosensitivity as a potential side effect.

3.3.6 Drug chemical structures

Exploring the molecular structures of drugs can lead to the identification of drugs with potential photoactivity for susceptible patients. However, if the drug is not in a closely related group, it is not necessarily possible to create a relationship between chemical structure and photobiological activity. For a drug to be regarded as a photosensitiser, it must absorb ultraviolet and/or visible radiation. The interaction between the drug and light leads to the generation of an excited state which in turn generates free radicals/superoxide anions (type I reaction) or singlet oxygen (type II reaction) (Aloisi et al., 2007, Schuch et al., 2017). The interaction between these ROS and their local microenvironment causes damage to critical cell components leading to a phototoxic response. A typical photosensitising drug would absorb UVR or visible radiation at wavelengths that can penetrate the skin, leading to the generation of high amounts of ROS that would then interact with other molecules, such as proteins (Hawkins et al., 2009), DNA (Lee and Kang, 2019) and lipids (Itri et al., 2014). Certain chemical structures are known to be more photolabile (susceptible to change on interaction with light), such as aromatic compounds (ring-shaped planar molecule) molecules that are conjugated with double bonds containing nitrogen, sulphur or oxygen, and drugs with chlorine substituents (Tamat and Moore, 1983). Of the DIP causative agents from our study quinine, thiazide, voriconazole, and PPI all fulfil the structural requirements of a potential photosensitizer (Table 3-15).

Table 3-15 Drug chemical structures

This table shows the chemical structures of drugs reported to induce photosensitivity in our data, namely: quinine, bendroflumethiazide, voriconazole, and omeprazole

Drug name	**Chemical structure**
Quinine	
Bendroflumethiazide	
Voriconazole	
Omeprazole	

Chlorine-containing drugs, such as hydrochlorothiazide, bendroflumethiazide, and quinine have aromatic chlorine substituent in their structure, which makes drugs in this group photoactive. Hydrochlorothiazide is one of the most frequently used diuretics and has been widely reported to induce DIP (Johnston et al., 2002, Gómez-Bernal et al., 2014, Blakely et al., 2019).

Bendroflumethiazide is another thiazide diuretic drug with a mechanism of action similar to hydrochlorothiazide (Duarte and Cooper-DeHoff, 2010, Shahin and Johnson, 2016). Irradiation of chlorine-containing drugs (designated as Aryl-Cl) causes photo-ionisation and bond dissociation (Tamat and Moore, 1983, Moore and Hemmens, 1982). Photo-ionisation is a process that leads to the formation of an ion by the physical interaction of a photon with an atom or molecule. Furthermore, the photolysis of these drugs in aqueous or alcoholic (R-OH) solutions leads to the liberation of hydrogen chloride (HCl) resulting in substitution (Aryl-OR) reduction (Aryl-H) of the original compound. Chlorine-containing drugs, such as hydrochlorothiazides have been shown to undergo photodechlorination to yield singlet oxygen when photolysed (Tamat and Moore, 1983).

Voriconazole's chemical structure contains several elements that can play a significant role in drug photosensitivity, including heterocyclic and polycyclic ring structures and halogenic residues. However, most azoles share the same characteristics and few adverse drug reactions have been reported when compared with voriconazole (Epaulard et al., 2011). The principal mechanisms for voriconazole-induced photosensitivity are yet unclear. It has been hypothesised that metabolites of voriconazole are photoactive and can absorb UVR and produce DIP. Hepatic metabolism of voriconazole occurs via P450 isoforms leading to eight major metabolites, the principal metabolite being N-oxide (Roffey et al., 2003, Alffenaar et al., 2010, Epaulard et al., 2011). Furthermore, it has been suggested that the N-oxide metabolite of voriconazole is responsible for phototoxic adverse reactions following absorption of UVB (range 290–340 nm) and UVC (range 235–290 nm) (Murayama et al., 2007). Voriconazole may, therefore, induce cellular DNA damage or interfere with its repair and this could lead to the clinical features of DIP (Haylett et al., 2013). Voriconazole further inhibits the production of cytochrome P450 enzyme; consequently, retinoid levels are elevated. Increased plasma level of all-trans-retinal has been reported in blood samples of patients who had facial erythema and cheilitis (Denning and Griffiths, 2001, Van Wauwe et al., 1990).

All PPIs have similar chemical structures, which are pyridine- and benzimidazole derivatives containing a sulphur moiety. PPIs are pro-drugs that needs to be activated by stomach parietal cells to the chemically active form: tetracyclic planar sulphonamide (Sachs et al., 1993). Metabolism of omeprazole leads to its main metabolites: sulphone, 5-hydroxy- and 5-O-desmethyl omeprazole.

Furthermore, all PPIs have a broadly similar mechanism of action with metabolism in the liver via cytochrome P450 isoforms, CYP2C19, and CYP3A4 (Stedman and Barclay, 2000, Äbelö et al., 2000). Searching the literature, few cases of photoallergic dermatitis were identified following PPI administration (Ricciardi et al., 2003, Dam and Bygum, 2008, Shukla et al., 2010). The mechanism by which PPIs induce photosensitivity has not yet been studied; however, it has been suggested that the sulphur moiety, common to all PPIs, may be responsible for this reaction (Shukla et al., 2010).

3.3.7 Dermatology Life Quality Index

Determining the impact of a disease on QoL is an important aspect in the dermatology field for many reasons. Firstly, skin disease has a significant impact on a patient's social life and psychological status. Secondly, QoL scores and physical assessment can be used to assess treatment efficacy (Drucker et al., 2017, Nagpal et al., 2019, Tribó et al., 2019).

A recent comprehensive review of the impact of photosensitivity on QoL reported a 'very or extremely large (DLQI > 10) impact in approximately one-third of adult surveys, in addition, level of anxiety and depression was reported to be double of U.K healthy population (Walburn and Sarkany, 2020, Rutter et al., 2020). There are relatively few reports examining the impact on the quality of life of exogenous drug-induced photosensitivity, Jong *et al.* (2008) reported 23% of 26 DIP patients had DLQI scores of greater than ten whilst a study by Rizwan *et al.* reported mean DLQI scores of 10.84 in eight patients (Jong et al., 2008, Rizwan et al., 2013).

This study had a higher response rate compare with Jong *et al.* (2008) study (65% versus 42% respectively) which may be attributable to patients being asked to complete the questionnaire at the time of photoinvestigation rather than responding to a postal questionnaire, larger sample size (122 versus 26 respectively) and the possibility that some of the DIP may had resolved by the time of the postal study. The results from this project, showed a greater impact on a patient's QoL compare with studies in the literature. The percentage of patients with DLQI >10 was 69% in this study compared with 23% of DIP patients in the multicentre study (Jong et al., 2008).

Rutter *et al.* (2020) highlight the difficulties associated with the potential seasonality of photodermatoses. The DLQI questionnaire evaluates the impact of the condition over the past week; thus, if the questionnaire is completed in winter, the impact may be lower than that seen at the height of summer. To overcome these studies have asked participants to review the impact of their symptoms over the last year with higher DLQIs reported for the 12-months compare to one-week for some photodermatoses (AP, CAD and SU) (Rutter et al., 2020, Rizwan et al., 2013, Stafford et al., 2010). However, in the case of DIP, median DLQI scores have been reported to be very similar when reviewed over 12 months versus seven days (median score 4 and 3 respectively) (Jong et al., 2008).

3.3.8 Study strengths and limitations.

The significant strength of this study was the large number of patients investigated over several years. The clinical evidence for DIP was studied in detail, including the photobiological characterisation of each drug, including monochromator phototest and provocation testing with two light sources (SSR and broadband UV-A).

There were, however, several limitations to this study. First, it is a retrospective study, although all patients underwent assessment according to standardised clinical and phototest protocols. This limited the data to that available in the medical records. As a result, we depended on existing medical notes to determine the prevalence of DIP in the Salford database. Secondly, a limitation of all studies of DIP is that no effective tests are available to prove beyond doubt that the DIP was caused by a specific drug in a specific patient. Thirdly, most of the patients were taking numerous medications, as a result of identifying the culprit drug was a challenge. Fourthly, most of the cases were diagnosed as a probable – not definite – case of DIP. One way to increase the confidence of a 'probable' diagnosis would be to re-evaluate the patient after six months without the medication to see whether symptoms had improved. Evaluation of the patients at six months after stopping the medication allows the clinician to determine whether the suspected drug was indeed the culprit. However, many patients either did not attend their follow-up appointment or chose to be treated locally. This is probably due to the considerable distance some patients had to travel as the photobiology unit accept referrals from across a large area of England.

3.3.9 Conclusion

Our data identified the prevalence of DIP to be 5.4% of photoinvestigations, showing that drug photosensitivity is a notable clinical problem. An almost similar number of males and females are affected overall (female patients represent 52.5% and male 47.5%). Whilst the older age group of adults was predominantly affected (median patient age, 62 years), a wider range of ages can be afflicted with DIP (age range 11 to 86 years). This study has confirmed that quinine and thiazide diuretics remained the commonest culprit drugs. Interestingly, the data highlights a developing issue, as DIP reactions occurred in 12 cases (9.8%). Where PPIs were the probable culprit drug. Clinically, sunburn-like reactions and photosensitive eczematous reaction were the noticeable adverse drug reaction. In addition, this study indicated that DIP has a remarkably high impact on the patient's QoL, so clearly demonstrating the need to establish effective management strategies to quickly diagnose the condition and provide appropriate to aid its resolution and so reduce its impact on QoL.

Chapter 4: Prevalence of drug-induced photosensitivity in the outpatients' clinics (community).

4.1 Introduction

Prevalence of DIP is unknown, and it can be underestimated for many reasons: frequency and duration of the taken medications, undiagnosed or underreporting of the DIP cases and absent of effective diagnostic test. In addition, new drugs are constantly being developed; for example, the FDA approves 40-50 drugs per year over the last five years (FDA, 2020). As a result, new drugs have been identified to caused DIP, however, there was a significant period between the drug development and the report of photosensitivity adverse effects, for example, a drug named brigatinib was approved in the United States (April 2017) but the first report of DIP was in 2019 (Markham, 2017, Morgado et al., 2019). However, systemic reviews usually can identify a range of medication causing DIP (Blakely et al., 2019, Kim et al., 2018). DIP prevalence predication studies usually retrospective studies and case reports; all these factors contribute to a lack of information related to DIP prevalence.

The number of medications taken by patients has a significant effect both in identifying the drug adverse effects and estimation of the prevalence of DIP. In 2015 an average of 18.6 items were prescribed per patients per years and this percentage is rising in areas of deprivation. For Salford and Eccles the prescribing rate found to be 22.9 items/head/year (Baker, 2016). There is a significant link between the number of medication and patient age, the number of medicines taken was reported to increase with age. Review of the yellow cards reported that adverse skin reactions were the most prevalent and incidents increase with age (Bem JL, 1988). Gender difference in drug prescribing has also been reported (Manteuffel et al., 2014, Morgado et al., 2019). In the UK number of potential photosensitisers is unknown, as a result, the potential problem unclear. As detailed above in the first study, DIP has a significant impact on QoL, and undetected patients may suffer. As a result, drug substitution would lead to alleviating the drug side effects. This study is a questionnaires-based study, which could play a significant role in the identification of the prevalence of DIP in the dermatology field.

The study aims to use a 13-based questionnaire to estimate the prevalence of DIP in the outpatient's clinics at Salford Royal NHS Foundation Trust, Manchester, UK. Second, to determine the demographic characteristics of those who were taking potential photosensitisers. Third, to identify the participants who were taking potential photosensitising medications as they considered to be at risk of developing DIP and classify them in groups: unlikely, possible and probable case of DIP. Finally, identify the most common culprit drugs that can lead to a probable case of DIP.

4.2 Response rate

The questionnaire was a face-to-face short time survey, with a total number of 986 participants approached, of which a total number of 531 agreed to fill the questionnaire; the response rate was 53.8%. The total number answering yes to question one (Are you taking any tablets or medicines?) was 475 (89.4%), with 56 responding that they were not taking any medications and therefore not required to answer any further questions.

4.3 Summary data for the 475 participants currently taking tablets or medicines

4.3.1 Demographic data

Demographic data for the 475 participants who reported that they were currently taking tablets or medicines shown in Table 4-1.

Table 4-1 Demographic data for the 475 participants who answered yes to Question 1: "Are you taking any tablets or medicines (prescription or over the counter)?"

Characteristics	**Total**	**Female**	**Male**
Number* (%)	475 (89.4%)	302 (63.6%)	172 (36.2%)
Mean Age (years)	64	63	65.6
Age range (years)	40–94	40–94	40–88

* Missing data on gender = 1

Analysis of the 475 participants' response to Question 2, which details skin phototype (Describe your skin response after been in the sun for 30 minutes at midday in June in England without sunscreen) and Question 3 (What was your natural hair colour), (Table 4-2).

Table 4-2 Number and percentage of skin phototype and natural hair colour of 475 participants

Phototype*	**Red**	**Blonde**	**Light brown**	**Dark brown/Black**
Type I (n=91; 19.1%)	13 (14.3%)	15 (16.5%)	35 (38.5%)	28 (30.8%)
Type II (n=162; 34.1%)	13 (14.3%)	24 (14.8%)	69 (42.6%)	56 (34.6%)
Type III (n = 171; 36%)	2 (1.2%)	24 (14%)	63 (36.8%)	82 (47.9%)
Type IV (n= 50; 10.5%)	1 (2%)	8 (16%)	19 (38%)	22 (44%)

* Missing data on skin type = 1

4.4 Identification and classification of medicines taken by 475 participants

Of the 475 who answered yes to Question 1 (‘Are you taking any medicines?’) in total 1416 medicines were being taken, some participants were receiving more than one medicine, and some medications were taken by many subjects; of these 716 (50.4%) medicines were photosensitisers. For the 475 participants, there were 211 different types of individual drugs taken, with 75 (35.5%) identified as potential photosensitisers (Table 4-3). The medicines were reviewed, and a list of potential photosensitising agents compiled which shown in (Table 4-4) and Appendix 5.

Table 4-3 Drug class and name of potential photosensitising agents identified (75) among the 211 medicines taken by 475 subjects who answered yes to question one and frequency of use

Drug class	**Potential photosensitising agents and frequency of use**
Antibiotics (6)	· **Tetracycline:** Doxycycline (3), Lymecycline (1) · **Sulfonamides derivates:** Sulfasalazine (1) · **Others**: Nitrofurantoin (1)
Antiarrhythmic (5)	Amiodarone (3), Dronedarone (2)
Anticonvulsants (30)	Pregabalin (25), Valproate (3), Lamotrigine (1), Phenytoin (1)
Antidiabetic agents (41)	Metformin (41)
Antidepressants (91)	· **SSRI antidepressant***: Citalopram (23), Sertraline (18), Fluoxetine (8), Paroxetine (1) · **Tricyclic antidepressant:** Amitriptyline (28), Mirtazapine (10), Nortriptyline (1) · **SNRI antidepressant*:** Venlafaxine (2)
Antihistamines (11)	Ranitidine (7), Chlorphenamine (3), Promethazine (1)

Drug class	Potential photosensitising agents and frequency of use
Antihypertensives (172)	· **ACEs***: Ramipril (39), Enalapril (2) · **ARB***: Losartan (13), Candesartan (10), Irbesartan (6), Telmisartan (1) · **CCBs** *: Amlodipine (51), Nifedipine (8), Diltiazem (5), Felodipine (3) · **Thiazide diuretic**: Bendroflumethiazide (16), Indapamide (4), Hydrochlorothiazide (1) · **Loop diuretic:** Furosemide (12) · **Potassium-sparing diuretic:** Spironolactone (1)
Antimalarials (12)	Hydroxychloroquine (9), Quinine Sulfate (3)
Antiretrovirals (2)	Acyclovir (1), Eviplera (1)
Antipsychotics (5)	· **Typical antipsychotic:** Quetiapine (2), Aripiprazole (1), Olanzapine (1) · **Thioxanthene antipsychotic**: Prochlorperazine (1)
NSAIDs (63)	Ibuprofen (28), Naproxen (27), Diclofenac (4), Mefenamic Acid (2), Sulindac (2)
Biologic (anti-TNF alpha) (2)	Infliximab (1), Adalimumab (1)
Chemotherapeutic Agent (25)	Methotrexate (25)
Cholesterol-lowering drugs (104)	Simvastatin (47), Atorvastatin (47), Pravastatin (4), Rosuvastatin (4), Fenofibrate (1), Fluvastatin (1)
Diuretic agents (34)	· **Thiazide diuretic:** Bendroflumethiazide (16), Indapamide (4), Hydrochlorothiazide (1) · **Loop diuretic:** Furosemide (12) · **Potassium-sparing diuretic:** Spironolactone (1)

Drug class	Potential photosensitising agents and frequency of use
Immunomodulator (10)	Sulfasalazine (6), Azathioprine (3), Mycophenolate (1)
Proton pump inhibitors (102)	Omeprazole (97), Esomeprazole (4), Pantoprazole (1)
Others	· **Adrenoreceptor blocker:** Tamsulosin (6) · **Anticholinergic:** Tiotropium (1) · **Anti-inflammatory:** Mesalazine (4) · **Antineoplastic:** Hydroxycarbamide (1) · **Antiplatelet:** Clopidogrel (15) · **Antifungals:** Terbinafine (1) · **Contraceptive hormones:** Ethinyl estradiol (1) · **Dopamine agonist:** Pramipexole (2) · **Monoclonal antibody:** Tocilizumab (1) · **Skin lightening agent:** Hydroquinone (1)

ACEs: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blocker, CCBs: Calcium channel blockers, SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin-norepinephrine reuptake inhibitor.

All 1,416 medicines were then reviewed, sorted into classes, and potential photosensitising medicines identified (Table 4-4). The number of occasions each drug was prescribed was calculated, and each class was expressed as a percentage of the whole (1,416 drugs). Within each class, the number of potential photosensitisers was also calculated.

Table 4-4 All 1,416 drugs taken by 475 participants

The drugs are classified by class, subclass, drug name and percentage of classes– the potential photosensitisers shown in Italics

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Antibiotics (10)		Benzathine (1) Penicillin (1) Teicoplanin (1) Azithromycin (1) *Doxycycline (3)* *Lymecycline (1)* *Nitrofurantoin (1)* *Sulfasalazine (1)*	0.71% *(0.42%)*
Antihypertensives (241)	Angiotensin-converting enzyme inhibitors (69)	Lisinopril (27) Trandolapril (1) *Enalapril (2)* *Ramipril (39)*	19.7 % *(12.6%)*
	Angiotensin receptor blocker (31)	Entresto (1) *Candesartan (10)* *Irbesartan (6)* *Losartan (13)* *Telmisartan (1)*	
	Calcium channel blockers (71)	Lercanidipine (1) Verapamil (3) *Amlodipine (51)* *Diltiazem (5)* *Felodipine (3)* *Nifedipine (8)*	

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
	Beta-blocker (55)	Atenolol (12) Bisoprolol (33) Metoprolol tartrate (1) Nebivolol (1) Sotalol (1) *Propanolol (7)*	
	Thiazide diuretic (21)	*Bendroflumethiazide (16)* *Hydrochlorothiazide (1)* *Indapamide (4)*	
	Loop diuretic (14)	Bumetanide (2) *Furosemide (12)*	
	Potassium-sparing diuretic (1)	*Spironolactone (1)*	
	Carbonic anhydrase inhibitor diuretic (2)	Acetazolamide (1) Benzthiazide (1)	
	Other (15)	Aldomin (1) Bosentan (1) Clonidine (2) Doxazosin (11)	
Antiarrhythmics (10)		Flecainide (2) Glyceryl Trinitrate (1) Isosorbide mononitrate (1) Ranolazine (1) *Amiodarone (3)* *Dronedarone (2)*	0.71% *(0.35%)*

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Nonsteroidal anti-inflammatory drugs (122)		Arcoxia (3) Aspirin (55) Etodolac (1) *Diclofenac (4)* *Ibuprofen (28)* *Mefenamic acid (2)* *Naproxen (27)* *Sulindac (2)*	8.6 % *(4.5%)*
Antipsychotics (9)	Typical antipsychotics (4)	*Aripiprazole (1)* *Olanzapine (1)* *Quetiapine (2)*	0.64% *(0.35%)*
	Serotonin 5 HT1 receptor agonists (2)	Sumatriptan (3) Zolmitriptan (1)	
	Thioxanthene antipsychotic (1)	*Prochlorperazine (1)*	
Antidepressants (96)	Serotonin-norepinephrine reuptake inhibitor (6)	Duloxetine (4) *Venlafaxine (2)*	6.8% *(6.4%)*
	Selective serotonin reuptake inhibitor (50)	*Citalopram (23)* *Fluoxetine (8)* *Paroxetine (1)* *Sertraline (18)*	
	Tricyclic antidepressants (39)	*Amitriptyline (28)* *Mirtazapine (10)* *Nortriptyline (1)*	
	Triazolopyridine antidepressant (1)	*Trazodone* (1)	

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Anticonvulsants (60)		Carbatrol (1) Clonazepam (1) Gabapentin (25) Levetiracetam (1) Topiramate (2) *Lamotrigine (1)* *Phenytoin (1)* *Pregabalin (25)* *Valproate (3)*	4.2% *(2.1%)*
Chemotherapeutic agents (25)		*Methotrexate (25)*	1.76% *(1.76%)*
Hypoglycaemics (3)		Glimepiride (1) Glipizide (2)	0.21% *(0%)*
Antidiabetic agents (54)	Gliptins (5)	Alogliptin (1) Anagliptin (1) Linagliptin (2) Liraglutide (1)	3.8 % *(2.9%)*
	SGLT2 inhibitors (2)	Canagliflozin (1) Empagliflozin (1)	
	GLP-1 receptor agonist	Dulaglutide (1)	
	Other (46)	Gliclazide (5) *Metformin (41)*	
Anticoagulants (19)		Acenocoumarol (2) Dalteparin (1) Heparin (1) Rivaroxaban (4) Warfarin (11)	1.3 % *(0%)*
Cholesterol-lowering agents (108)		Ezetimibe (4) *Atorvastatin (47)* *Fenofibrate (1)* *Fluvastatin (1)* *Pravastatin (4)* *Rosuvastatin (4)* *Simvastatin (47)*	7.6 % *(7.3 %)*

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Antihistamines (25)		Cetirizine (3) Cyclizine (1) Fexofenadine (3) Loratadine (7) *Chlorphenamine (3)* *Promethazine (1)* *Ranitidine (7)*	1.76% *(0.78%)*
Antimalarials (12)		*Hydroxychloroquine (9)* *Quinine (3)*	0.85% *(0.85%)*
Antifungals (2)		Posaconazole (1) *Terbinafine (1)*	0.14% *(0.07%)*
Antiretrovirals (1)		*Acyclovir (1)*	0.07% *(0.07%)*
Hormones (87)		Budesonide (1) Finasteride (3) Hydrocortisone (1) Insulin (3) Prednisolone (13) Seretide (6) Somatropin (1) Symbicort (1) Thyroxine (57) *Estradiol (1)*	6.14% *(0.07%)*
Immunomodulators (11)		Copaxone (1) *Azathioprine (3)* *Mycophenolate (1)* *Sulfasalazine (6)*	0.78% *(0.7 %)*
Opioids (90)		Buprenorphine (1) Codeine (17) Codeine and paracetamol (38) Fentanyl (1) Morphine (3) Oxycodone (7) Tramadol (23)	6.3% *(0%)*

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Proton Pump Inhibitors (132)		*Esomeprazole (4)* Lansoprazole (28) Latanoprost (2) *Omeprazole (97)* *Pantoprazole (1)*	9.3% *(7.2%)*
Vitamins & Supplements (40)		Bioflavonoids (1) Cholecalciferol & Calcium (8) Cholecalciferol (12) Folic acid (11) Forceval (1) Fortamind (1) Glucosamine (1) Green Tea (1) Sodium Chloride (1) Thiamine (2) Turmeric (1)	2.8% *(0%)*
H1 receptor agonist (1)		Betahistine (1)	0.07% *(0%)*
Adrenergic agonist (1)		Mirabegron (1)	0.07% *(0%)*
Alcohol Agonist (1)		Disulfiram (1)	0.07% *(0%)*
Adreno-receptor blocker (8)		Alfuzosin (1) Timoptol (1) *Tamsulosin* (6)	0.56% *(0.4%)*
Analgesics (37)		Nefopam (1) Paracetamol (36)	2.6% *(0%)*
Antacid (1)		Gaviscon (1)	0.07% *(0%)*
(Biologic) Anti-TNF alpha (2)		*Infliximab* (1) *Adalimumab* (1)	0.14% *(0.14%)*
Anti-inflammatory (5)		*Mesalazine* (5)	0.35% *(0.35%)*

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Antioestrogen (3)		Tamoxifen (3)	0.21% *(0%)*
Antiretroviral (1)		*Eviplera (Emtricitabine/Rilpivirine /Tenofovir)* (1)	0.07% *(0.07%)*
Anti-cholinergic (2)		Trelegy Ellipta (1) *Tiotropium* (1)	0.14% *(0.07%)*
Anti-diarrhoeal (5)		Loperamide (5)	0.35% *(0%)*
Anti-muscarinic (1)		Solifenacin (1)	0.07% *(0%)*
Antineoplastics (1)		*Hydroxycarbamide* (1)	0.07% *(0.07%)*
Anti-platelet agent (15)		*Clopidogrel* (15)	1.06% *(1.06%)*
Anti-spasmodic (5)		Buscopan (5)	0.35% *(0%)*
Hormone therapy – aromatase inhibitors (4)		Exemestane (1) Letrozole (3)	0.28% *(0%)*
Benzodiazepines (5)		Diazepam (3) Nitrazepam (1) Zopiclone (1)	0.35% (0%)
Bile acid (1)		Ursodeoxycholic acid (1)	0.07% *(0%)*
Bile Sequestrant (1)		Colesevelam (1)	0.07% *(0%)*
Biphosphonates (7)		Alendronic acid (5) Biphosphonate (1) Risedronate (1)	0.49% *(0%)*
Bronchodilator (2)		Salbutamol (2)	0.14% *(0%)*
Cardiac glycoside (2)		Digoxin (2)	0.14% *(0%)*

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Cholinesterase Inhibitor (2)		Donepezil (2)	0.14% *(0%)*
Dopamine agonist (2)		*Pramipexole* (2)	0.14% *(0.14%)*
Dopamine precursor (1)		Stalevo (1)	0.07% *(0%)*
Anticlotting agents (2)		Apixaban (2)	0.14% *(0%)*
HCN channel blocker (1)		Ivabradine (1)	0.07% *(0%)*
Peripheral vasodilator (1)		Pentoxifylline (1)	0.07% *(0%)*
Laxative (14)		Bisacodyl (1) Docusate (4) Lactulose (1) Macrogol (4) Senna (4)	0.99% *(0%)*
Leukotriene receptor antagonist (1)		Montelukast (1)	0.07% *(0%)*
MAOI/anti-Parkinson's agent (1)		Selegiline (1)	0.07% *(0%)*
Monoclonal antibody (7)		Etanercept (2) Mepolizumab (1) Rituximab (3) *Tocilizumab* (1)	0.49% *(0.07%)*
Mucolytics (5)		Carbocisteine (5)	0.35% *(0%)*
NMDA receptor antagonist (1)		Memantine (1)	0.07% *(0%)*

Class (Number of class prescribed)	**Subclass (Number of subclass prescribed)**	**Drug name (Number of drugs prescribed)**	**Percentage of class *(Percentage of photosensitisers within the class)***
Opioid agonist-antagonist (1)		Buprenorphine (1)	0.07% *(0%)*
Dopamine receptor antagonist (1)		Metoclopramide (1)	0.07% *(0%)*
Skin lightening agent (1)		*Hydroquinone* (1)	0.07% *(0.07%)*
Thiazolidinediones (3)		Pioglitazone (3)	0.21% *(0%)*
Xanthine oxidase inhibitor (14)		Allopurinol (14)	0.99% *(0%)*
Participants unable to remember the name of the medicine (54)			3.80%

4.5 Relationship between medicines and demographic data for the 475 participants

The mean number of medications taken by each subject was 2.99 (range = 1–9). Of the 475 participants, 361 were taking a potential photosensitiser. The mean number of potential photosensitising agents taken was 1.51 (range 1–6) and non-photosensitising agents the mean was 1.36 (range 1–7). In terms of gender, the mean number of drugs taken by women was 3.01 (range 1–9) compared to 2.97 (range 1–9) in men. In terms of potential photosensitisers, women took on mean 1.55 (range 1–6) and men 1.46 (range 1–6). Women on mean took 1.36 (range 1–7) non-photosensitising drugs whilst men took 1.37 (range 1–7). Table 4-5 shows the mean number of medications taken by each age group. The number of medicines taken increased with age.

Table 4-5 Mean number of medications taken by the 475 participants: age range and all medications, potential photosensitisers and non-photosensitisers

Mean (range) number of medicines taken			
Age (years)	**All medications**	**Potential photosensitisers**	**Non-photosensitisers**
40–49	1.98 (0–9)	1.02 (0–5)	0.88 (0–4)
50–59	2.93 (0–9)	1.63 (0–6)	1.25 (0–7)
60–69	2.86 (0–8)	1.4 (0–6)	1.3 (0–7)
70–79	3.32 (0–9)	1.58 (0–6)	1.57 (0–5)
80–89	3.83 (0–9)	2 (0–5)	1.91 (0–5)
90–99*	2	0	2

*The 90–99 age category included only one individual

The most frequently taken classes of drugs (expressed as a percentage of the 1,416 total medicines taken) and the corresponding frequency of potential photosensitisers within each class shown in (Table 4-6). As can be seen, for five of the top classes of medicine (together representing 52.1% of drugs taken), the prevalence of potential photosensitisers is more than a third (38%).

Table 4-6 Summary of frequency of the classes of drugs, and potential photosensitisers within each class, were taken by the 475 participants

Values are expressed as a percentage of 1,416 drugs taken. Drug classes that constitute less than 1% of drugs taken are shown in Table 4-4

Class of drug	**Frequency of the classes of drugs (%)**	**Frequency of potential photosensitisers within the class (%)**
Anti-hypertensive	19.7%	12.6 %
Proton pump inhibitor	9.32%	7.2%
Non-steroidal anti-inflammatory drug	8.62%	4.45%
Cholesterol-lowering agents	7.63%	7.34%
Antidepressants	6.8%	6.4%
Opioids	6.36%	0%
Hormones	6.14%	0.07%
Anticonvulsant	4.2%	2.12%
Antidiabetic	3.81%	2.89%
Vitamins & supplements	2.8%	0%
Analgesics	2.61%	0%
Antihistamine	1.76%	0.78%
Chemotherapeutic agents	1.76%	1.76%
Anticoagulants	1.34%	0%
Antiplatelet	1.06%	1.06%

4.6 Responses to questions 4 and 5: identifying potential drug-induced photosensitivity

Questions 4 and 5 were the key questions in the questionnaire; Q4 asked the participant if they experienced redness and/or a burning feeling on the skin following sun exposure that they did not think was normal sunburn. While, Q5 asked if it was more severe than sunburn experienced by their friends and family. Based on the participants' answers to Questions 4 and 5, the results were classified into two categories: possible DIP or unlikely DIP. If the participant answered 'yes, I do currently' and/or 'yes, in the past' the response was considered as a possible case of DIP. Of the 475 patients who answered yes to question 1 ('yes, I am taking medications'), 139 (29.3%) answered yes currently and/or yes in the past to Question 4 and/or Question 5. If the subject answered no and/or do not know, we considered this case as unlikely to be DIP and no further analysis was performed. Table 4-7 breaks down the responses to Questions 4 and 5 for the 475 who were taking medication.

Table 4-7 The 475 participants' responses to Questions 4 and 5 as a whole and by sex

Question number	**Sex**	**Yes, currently**	**Yes, in past**	**No**	**Don't know**
Question 4	All (n=475)	73 (15.8%)	52 (10.9%)	328 (69%)	22 (4.6%)
	Female (n=302)	47 (15.6%)	33 (10.9%)	205 (67.9%)	17 (5.6%)
	Male (n=172)	26 (15.1%)	19 (11.05%)	122 (70.9%)	5 (2.9%)
Question 5	All (n=475)	57 (12%)	37 (7.8%)	360 (75.8%)	21 (4.4%)
	Female (n=302)	40 (13.2%)	25 (8.3%)	225 (74.5%)	12 (3.9%)
	Male (n=172)	17 (9.9%)	12 (6.98%)	134 (77.9%)	9 (5.2%)

4.7 Identification of potential photosensitisers: 112 participants

The medications listed by 139 participants who answered ‘yes currently’ or ‘yes, in the past’ to Question 4 and/or Question 5 were examined, and any potential photosensitisers identified. Of 139 who were classified as possible cases of DIP, based on their response to Q4 and/or Q5, 112 (80.1%) were identified as having received drugs which have been associated with DIP. A further 19 participants were not taking any known photosensitiser and eight could not remember their medications. Seven participants who believed that they had had a more severe response than their family or friends (Q5) did not think this was abnormal (i.e., responded ‘No’ to Q4). Similarly, 31 participants who believed that their response was abnormal (Q4) did not think that it was more severe than that of their friends and family. The 112 participants’ responses to Q4 & Q5 are shown in Table 4-8.

Table 4-8 The 475 participants’ responses to Q4 and Q5 of participants taking a known photosensitiser (n = 112)

	Q5			
Q4	Yes	Yes, in the past	No	Do not know
Yes	36	4	11	7
Yes, in the past	3	16	20	1
No	2	5	0	0
Do not know	4	3	0	0

4.7.1 The demographic characteristics of the 112 participants

Demographic data of the 112 participants who were taking potential photosensitisers shown in (Table 4-9).

Table 4-9 Demographic data of the 112 participants': age, sex, and sun-reactive skin type (n = 112)

Characteristics	**Total**	**Female**	**Male**
Number (%)	112	73 (65.2%)	39 (34.8%)
Mean Age (years)	62.1	59.5	67
Age range (years)	45–88	45–87	48–88
Skin phototype I	40	28	12
Skin phototype II	40	27	13
Skin phototype III	28	15	13
Skin phototype IV	3	3	0

The number of medications taken by the 112 participants shown in (Table 4-10). The mean number of medications taken was 3.72. No significant difference was observed between the number of all medicines taken by men and by women (mean 3.8 and 3.7, respectively); however, there was a significant difference between the mean number of potential photosensitisers taken by men and by women (3.8 and 6.9 respectively).

Table 4-10 Total numbers of medicines and potential photosensitisers taken by the 112 subsets

Number of medications taken	**Participants taking this number of medicines among the sample population (n = 112)**	**Participants taking this number of *potential photosensitisers* among the sample population (n = 112)**
1	15	51
2	23	30
3	20	16
4	19	12
5	14	3
6	9	-
7	4	-
8	4	-
9	4	-

Table 4-11 shows the numbers of medications (mean) taken by age group. The number of medications taken by the youngest group (40–49 years) was lower than that of the oldest age group (80–89 years. There was no correlation between the number of potential photosensitisers taken and age (Spearman's correlation coefficient r = 0.3).

Table 4-11 Mean number of medicines and potential photosensitisers taken per age group by the 112 subsets

Age group (years)	**Mean number of medicines**	**Mean number of potential photosensitisers**
40–49	2.55	1.5
50–59	3.92	2.06
60–69	3.83	1.96
70–79	3.52	1.84
80–89	4.17	2

The number of potential photosensitising medications taken are shown by their generic name and grouped into their respective classes in Table 4-12.

Table 4-12 The potentially photosensitising medications, a total of 230 taken by 112 participants, were classified in groups based on their therapeutic class and generic name

Class	Drug Name
Anti-hypertensive (58)	· **CCBs*:** Amlodipine (17), Nifedipine (4), Diltiazem (3) · **B B***: Propranolol (2) · **ACEs*:** Ramipril (12), Enalapril (2) · **ARBs*:** Losartan (5), Irbesartan (3), Candesartan (1), Telmisartan (1) · **Thiazide Diuretic**: Bendroflumethiazide (6), Indapamide (1) · **Loop Diuretic:** Furosemide (1)
PPI* (28)	Omeprazole (28)
Anti-depressant (33)	· **Tricyclic Antidepressant**: Amitriptyline (11), Mirtazapine (6) · **SSRI* Antidepressant:** Citalopram (6), Sertraline (5), Fluoxetine (3) · **SNRI *Antidepressant:** Venlafaxine (2)
Cholesterol-Lowering Drugs (300)	Simvastatin (15), Atorvastatin (14), Rosuvastatin (1)
Chemotherapeutic Agent (17)	Methotrexate (17)
Hypoglycaemic (14)	Metformin (14)
NSAIDS* (15)	Ibuprofen (9), Naproxen (4), Diclofenac (1), Sulindac (1)
Anti-malarial (10)	Hydroxychloroquine (9), Quinine Sulfate (1)
Anti-convulsant (6)	Pregabalin (6)

Class	Drug Name
Aminosalicylates (3)	Sulfasalazine (2), Mesalazine (1)
Anti-histamines (2)	Promethazine (1), Chlorphenamine (1)
Anti-arrhythmic (1)	Dronedarone (1)
Others	· **Alpha-adrenergic blocker:** Tamsulosin (3) · **Antiplatelet agent:** Clopidogrel (3) · **Hormones:** Hormone Replacement Therapy (2) · **Immunosuppressant:** Azathioprine (2) · **Tetracycline antibiotics:** Doxycycline (1) · **Antifungal:** Terbinafine (1) · **Dopamine agonists:** Pramipexole (1) · **Tumour necrosis factor blocker:** Adalimumab (1)

ACEs: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin receptor blocker, BB: Beta-blocker: CCBs: Calcium channel blockers, NSAID: Non-steroidal anti-inflammatory drug, PPI: Proton pump inhibitor, SSRI: Selective serotonin reuptake inhibitor, SNRI: Serotonin-norepinephrine reuptake inhibitor

4.8 Data analysis of question 6: How old were you when the redness/burning feeling in the sun appeared for the first time?

4.8.1 Temporal relationship between commencing medication and the onset of symptoms

Question 6 asked the participants to identify the age at which they first noticed an abnormal burning response to light (Q6: How old were you when the redness/burning feeling in the sun appeared for the first time?). Using responses to Question 6 and the patient's age it was possible to calculate the year in which their abnormal burning symptoms started. This was then cross-referenced with the subject's responses to Q1 ('please list the name of each medication below and the year you started taking it.'). This step was to determine which medications were being taken before their burning symptoms began (as medications started after their burning symptoms began were unlikely to be related). Question 6 was commonly misinterpreted by participants with many responding with the duration rather than their age so, for example, subject 22 aged 60 responded 'one year' to the age at which they first noticed an abnormal burning response. On clarification, it became clear that this was the number of years their abnormal burning symptoms had been present. Ten participants were found to have started their medication before their symptom started (Table 4-13) this represents 2.1% of the 475 participants taking medicines and 1.89% of all participants agreeing to complete the questionnaire (n=531).

Table 4-13 Temporal relationship between medicines and the onset of symptoms (Q6: How old were you when the redness/burning feeling in the sun appeared for the first time?)

Question 6	**Number of participants (%)**
Medication started before burning symptoms	10 (8.9%)
Medication started after burning symptoms	55 (50.9%)
Unable to recall medication start date	22 (19.6%)
No answer to question 6	21 (18.7%)

The data analysis found ten participants: eight females with an age range of 49 to 78 years. The number of potential photosensitising medications taken by the ten participants ranged from one to six potential photosensitisers, with 34 potential photosensitisers being taken in total. For each of the ten participants, the potentially photosensitising drug/s that were started before the onset of symptoms were identified (in italics: Table 4 14). The most frequent drug identified as the culprit photosensitisers was the proton pump inhibitor omeprazole, which was identified as the potential culprit in five cases. In terms of drug classes, the anti-hypertensives were the most frequently suspected with four drugs identified (Amlodipine, Diltiazem, Irbesartan and Ramipril). The mean duration of the redness/burning symptoms among this group of 10 participants was 8.9 years (range 2–19 years) (Table 4-15).

Table 4-14 Details of the ten participants whose medication was temporally related to their symptom. Potential photosensitisers are in *Italics*

Age	Gender	Medication
57	F	Amitriptyline, *Citalopram* Gabapentin, *Metformin*, *Omeprazole*, Paracetamol, *Ramipril*, *Simvastatin*, Tramadol
78	F	Alendronic Acid, *Amlodipine*, Aspirin, *Simvastatin*,
49	F	Etodolac, *Omeprazole*, *Methotrexate*, Rituximab, *Sertraline*
59	F	*Amlodipine*, *Atorvastatin*, Aspirin, Cetirizine, Gabapentin, Lisinopril, *Naproxen*, *Terbinafine*
51	F	*Amlodipine*, *Citalopram*, *Omeprazole*
51	F	*Azathioprine*, *Hydroxychloroquine*
53	F	Codeine, Cylclizine, Gabapentin, *Omeprazole*, Morphine *Mycophenolate*
67	M	Aspirin, Azathioprine, *Diltiazem*, Quinine *Sulphate*, *Indapamide*, *Irbesartan*, *Simvastatin*
59	F	Atorvastatin, Buscopan, Hydroxyzine, *Omeprazole*, Prednisolone
52	M	*Atorvastatin*, Glipizide, *Metformin*, *Ramipril*, *Sertraline*

Table 4-15 Relationship between photosensitiser and onset of symptoms. Drugs started before the onset of symptoms are in italics

Potential Photosensitisers and date participants started taking medication	**Symptoms start year**	**The average duration (years) of redness/burning symptoms**
Citalopram: 2000 Omeprazole: 2008 Simvastatin & Amitriptyline:2013 Metformin: 2016 Ramipril: 2017	2007	11
Simvastatin & Amlodipine: 2006	2008	11
Omeprazole: 2003 *Methotrexate: 2008* *Sertraline: 2013*	2013	5
Naproxen:1999 Atorvastatin: 2008 Terbinafine: 2017	1999	19
Amlodipine & Citalopram: 2014 *Omeprazole: 2015*	2016	3
Azathioprine & Hydroxychloroquine: 2016	2016	3
Omeprazole: 2014 Mycophenolate: 2018	2016	2
Azathioprine, Diltiazem, Quinine Sulphate, Indapamide, Irbesartan, Simvastatin: 2000	2000	18
Atorvastatin: 2009 *Omeprazole: 2014*	2016	3
Metformin: 1994 Ramipril: 2004 Atorvastatin & Sertraline: 2008	1994	14

To calculate the potential rate of DIP among the 475 participants for each of the drugs suspected in the n=10 participants, the number of cases in the n=10 group was expressed as a percentage of the total number of participants (n=475) taking that drug (Table 4- 4). Azathioprine and quinine sulphate were associated with a particularly high number as only three participants were taking these drugs among the n=475 group. This can be compared with omeprazole and metformin which although taken by 97 and 41 participants respectively were associated with suspected DIP in only two and five cases giving a potential incidence rate of 5.1 and 4.9% Table 4-16.

Table 4-16 The photosensitisers identified as being associated with probable DIP expressed as a percentage of the number of the participants taking that drug among the 475 participants

Class	**Drug**	**Number probable DIP participants (n=10) taking the drug**	**Number of participants (n=475) taking potential photosensitiser**	**Probable DIP cases as a percentage of all taking that drug (%)**
Antidepressant	Citalopram	2	23	8.7
	Sertraline	2	18	11.1
Antihypertensive	Amlodipine	2	51	3.9
	Diltiazem	1	5	20
	Irbesartan	1	6	16.7
Antimalarial	Hydroxychloroquine	1	9	11.1
	Quinine	1	3	33.3
Chemotherapeutic agents	Methotrexate	1	25	4
Cholesterol-lowering agents	Atorvastatin	3	47	6.4
	Simvastatin	3	47	6.4
Diuretic	Indapamide	1	4	25
Hypoglycaemics	Metformin	2	41	4.9
Immunosuppressant	Azathioprine	2	3	66.7
NSAID	Naproxen	1	27	3.7
PPI	Omeprazole	5	97	5.1

4.9 The severity of response (Questions 7, 8, 9 and 10)

Of the ten participants identified as a probable case of DIP (i.e. had started their medication before the onset of their symptoms), the severity of their response was evaluated by their answers to Questions 7, 8, 9 and 10. These results were then compared against the responses of the subset (n = 112) who self-identified as having a response that was not normal (Q4) and/or a response worse than family and friends (Q5). For comparison, the results for the participants who were not taking a known photosensitiser are also shown (n = 19).

4.9.1 Response to Question 7: In spring/summer, is your redness/burning feeling?

Question 7 focused on whether the condition was worse in the summer (In spring/summer compared to winter, is your redness/burning feeling better, worse, the same or do not know?). As more UVR radiation is present in the spring/summer and people are more likely to go outdoors, it was hypothesised that participants with suspected DIP would report a worsening of their symptoms. Table 4 17 summarises the results and as can be seen, the subset whose potential photosensitising medications corresponds to their onset of symptoms (n =10) do indeed report a higher incidence of redness/burning in the summer than the other two subsets.

Table 4-17 Relationship between the worsening of redness/burning in spring/summer (Question 7) and the three subsets.

The 112 participants; the response was not normal to Question 4 and/or Question 5, the 19 participants; who were not taking a known photosensitiser and the ten participants who were identified as a probable case of DIP

	Redness/burning better in spring/summer	**Redness/burning worse in spring/summer**	**Redness burning same all year round**	**Don't know**
Abnormal sun response and temporal relationship with potential photosensitiser (n = 10)	1 (10%)	8 (80%)	0	1 (10%)
Abnormal sun response but no temporal relationship with photosensitiser (n = 112)	11 (9.8%)	64 (57.1%)	22 (19.6%)	14 (12.5%)
Abnormal sun response but not taking any known potential photosensitiser (n = 19)	4 (21%)	8 (42%)	6 (31%)	1 (5%)

4.9.2 Response to Question 8: On a sunny day, is your redness/burning feeling?

Question 8 asked the participants to consider their redness/burning feeling on a sunny day. Again, more severe photosensitivity would be expected to be associated with a more marked response on a sunny day. Table 4-18 summarises the responses reported. For the participants taking a potential photosensitiser that was temporally correlated with the onset of the redness/burning 90% reported a worsening on a sunny day compared with 47.3% of those not taking any known potential photosensitiser.

Table 4-18 Relationship between redness/burning and a sunny day (Question 8) for the three subsets

The 112 participants; response was not normal to Question 4 and/or Question 5, the 19 participants; who were not taking a known photosensitiser and the ten participants who were identified as a probable case of DIP

	Redness/burning better on a sunny day	**Redness/burning worse on a sunny day**	**Redness/burning same on a sunny day**	**Don't know**
Abnormal sun response and temporal relationship with potential photosensitiser (n = 10)	0	9 (90%)	0	1 (10%)
Abnormal sun response but no temporal relationship with photosensitiser (n = 112)	0	68 (60.7%)	31 (27.7%)	12 (10.7%)
Abnormal sun response but not taking any known potential photosensitiser (n = 19)	2 (10.5%)	9 (47.3%)	7 (36.8%)	1 (5.3%)

4.9.3 Response to Questions 9 and 10

Questions 9 and 10 address protective measures against sun exposure. Question 9 asked about the effects of sunscreen on the participant's symptoms (redness/burning). Typically, sunscreen use might be expected to improve symptoms and certainly, for the group not taking any known potential photosensitising agent (n=19) this seems to be the case with 78.9% reporting an improvement in symptoms. However, in the subset taking a known photosensitiser that is associated with symptoms (n=10), only 40% say an improvement with sunscreen whilst 50% reported no change (Table 4-19).

Table 4-19 Relationship between sunscreen use (Question 9) and redness/burning for the subsets for the three subsets

The 112 participants; response was not normal to Question 4 and/or Question 5, the 19 participants; who were not taking a known photosensitiser and the ten participants who were identified as a probable case of DIP

	Redness/burning better with sunscreen	**Redness/burning worse with sunscreen**	**No change in redness/burning with sunscreen**	**Don’t know**
Abnormal sun response and temporal relationship with potential photosensitiser (n = 10)	4 (40%)	0	5 (50%)	1 (10%)
Abnormal sun response but no temporal relationship with photosensitiser (n = 112)	67 (59.8)	1 (0.9%)	30 (26.8%)	13 (11.6%)
Abnormal sun response but not taking any known potential photosensitiser (n = 19)	15 (78.9%)	0	1 (5.3%)	3 (15.8%)

Question 10 evaluates the effects of clothing on participants' symptoms asking whether being covered with clothing makes the redness/burning symptoms better or worse. As might be expected, the majority of participants see an improvement in their symptoms if covered with clothing. However, 20% of the n=10 subset reports their redness/burning symptoms are unaffected by clothing, Table 4-20.

Table 4-20 Relationship between clothing (Q10) and the redness/burning of the three subsets

The 112 participants; response was not normal to Question 4 and/or Question 5, the 19 participants; who were not taking a known photosensitiser and the ten participants who were identified as a probable case of DIP

	Redness/burning better with clothing	**Redness/burning worse with clothing**	**Redness/burning unaffected by clothing**	**Don't know**
Abnormal sun response and temporal relationship with potential photosensitiser (n = 10)	7 (70%)	0	2 (20%)	1 (10%)
Abnormal sun response but no temporal relationship with photosensitiser (n = 112)	72 (64.3%)	64 (1.8%)	22 (19.6%)	15 (13.4%)
Abnormal sun response but not taking any known potential photosensitiser (n = 19)	17 (89.5%)	0	2 (10.5%)	0

4.10 Discussion

4.10.1 Prevalence of DIP and use of potential photosensitisers

Participants involved in this study were taking 1416 medicines, of which 716 (50.4%) were potential photosensitisers. This is very similar to values by Hofmann *et al* (2020) who reported potential photosensitisers making up an average of 49.5% of all prescriptions issued in Germany and 48.2% in Austria between 2010 and 2017 (Hofmann et al., 2020). In total, 211 different individual drugs were taken by the 475 participants and of these 75 (35.5%) potential photosensitisers were identified. A questionnaire-based survey of 356 older patients in Poland reported potential photosensitisers as making up 22.4% of the 152 different drugs taken (Korzeniowska et al., 2019). Comparison of the range of potential photosensitisers prescribed to these older Polish patients shows a narrower range of drugs being prescribed with only 16 cardiovascular versus in this study 22 and tend central nervous system drugs versus our 13. The lower number of potential photosensitisers prescribed may therefore reflect differences in healthcare systems and prescribing practices in Poland versus the UK.

Amongst the 475 who answered ‘yes’ to Question 1 (Are you taking any tablets or medicines?) the average number of potential photosensitisers taken was higher in the older aged group (80-89 years) compare with the younger group (40-49 years). This finding is similar to that of Korzeniowska *et al* (2019) as they found that the number of medications taken increased as the patients got older (Korzeniowska et al., 2019). Aged populations are more likely to use a significantly higher number of medications compared with younger ones; as a result, these individuals may be more at risk of DIP (Trakatelli et al., 2009, Gould et al., 1995).

The results in this study showed that 361 (76%) were taking a potential photosensitiser out of 475. Questions 4 & 5 were designed to identify the “possible” cases of DIP; and a total number of 139 participants (29.3%) answered ‘yes, currently’ and/or ‘yes, in the past’ to these questions. Two hundred and twenty-two participants who were taking a potential photosensitiser did not report responses to sunlight that they considered atypical (discussed below). Further analysis showed 112 participants - representing 23.6 % of the total 475 - were receiving a potential photosensitiser; these cases were classified as possible DIP.

Of these112 possible case of DIP, ten (2.1%) were identified as being probable DIP, characterised by a temporal link between starting their medications and the appearance of redness and/or experiencing a burning feeling (Question 6). Each of these participants was taking between one and six potential photosensitisers with 15 different drugs represented.

Reviewing the literature, the rate of the DIP has been reported from multiple centres worldwide with reported rates ranging from 1.9% to 14.5%. An older study evaluating photosensitivity in 203 patients in an academic medical centre (United States), reported that systemic DIP accounted for 7 % of cases, although no specific responsible medication names were given (Fotiades et al., 1995).

A retrospective study of 116 patients diagnosed with photodermatoses conducted at a Singapore skin referral centre reported systemic DIP to be 11.3%, making up 0.014% of all skin centre referrals over three years. This study reports nine drugs most commonly associated with DIP in their patients (chlorpromazine, promethazine, thioridazine, prochlorperazine, griseofulvin, doxycycline, tolbutamide, glibenclamide and thiazides) (Khoo et al., 1996); however, amongst the 475 participants in this study only four of these medicines were being taken (doxycycline, prochlorperazine, promethazine and thiazides), none of which were associated with probable DIP. This may represent changes in prescribing practices since this study was published for example, drugs such as thioridazine have since been withdrawn from the market (Bisset, 2002).

A retrospective study of adverse drug reactions reported to the Norwegian Adverse Drug Reactions Committee found that DIP reactions represented 8% of adverse drug reactions (Selvaag, 1997). This study showed that the tetracycline antibiotics were the most frequent class to cause photosensitivity reactions followed by diuretics and antihypertensive agents.

As in the findings presented here doxycycline was the tetracyclines most frequently associated with DIP, however, in terms of diuretics and anti-hypertensive agents' hydrochlorothiazide and enalapril were the most frequent compared to amlodipine and bendroflumethiazide reported here (Selvaag 1997).

A retrospective study conducted between 1990 and 2000 at a photodermatology referral centre in Greece, of 310 patients diagnosed with idiopathic photodermatoses 4.8%, photosensitive drug eruptions. The authors note that despite the assumption that most Greeks are considered to have darker skin, a substantial percentage of the population have a light-skinned complexion resulting in "not infrequent" diagnoses of photosensitivity.

The authors reported that hydrochlorothiazide was taken by 4 of the 15 DIP patients but did not provide any further details of culprit drugs (Stratigos et al., 2003). Hydrochlorothiazide was the least common thiazide (n=1) taken by the 475 participants with the potential photosensitiser bendroflumethiazide the most common (n=16).

Another study conducted by an Australian photodermatology clinic of 397 patients diagnosed with photosensitivity disorders between 1993 and 2000 reported that photosensitive systemic phototoxic drug reactions were found to be 2.1 %. However, no details of culprit drugs were given (Crouch et al., 2003).

A further study was performed between 2000 and 2001 of 141 Asians attending the Singapore clinic, systemic DIP was found to be up 14.5% of diagnoses. Fourteen suspected culprit drugs were identified of which the antihypertensive drugs, mainly hydrochlorothiazide, were the most frequently reported culprit drugs (Wong and Khoo, 2005). As with the earlier paper Khoo *et al*.(1996), the range of drugs identified was different to that found in results in this study with only four drugs (hydrochlorothiazide, metformin, fenofibrate and simvastatin) reported both in their study and had been taken by 475 participants in this study. The authors note that the use of "seemingly old-fashioned" drugs may be due to the healthcare system in Singapore where healthcare costs are largely borne by the individual (Wong and Khoo, 2005).

A study of 280 patients with photodermatoses carried out between 1997 and 2004, found no significant difference between DIP rates amongst African Americans and Caucasian patients (13.3 % vs 10.7%). Details of the culprit drugs were not given (Kerr and Lim, 2007).

However, a follow-on study to that Kerr and Lim 2007, found a significant difference in the rates of DIP between African American and Caucasian patients (0.7% versus 15.9%). The authors speculate that this may reflect the relative protective effect of skin pigmentation on phototoxicity (Nakamura et al., 2014).

Patel and Marfatia (2008) - in a prospective study carried out between 1997 -2006 reported photosensitive reaction in 2% patients presenting with adverse cutaneous drug reactions with ciprofloxacin and sparfloxacin identified as culprit drugs (Patel and Marfatia, 2008). Sparfloxacin has since been withdrawn from the USA due to its side effects (Qureshi et al., 2011).

Saha *et al*. (2012) reported phototoxicity in two (3.8 %) of patients attending the outpatient's department of a tertiary care hospital in India. The culprit drugs were described as an analgesic and a thiazide (Saha et al., 2012).

A study by the India Institute of Medical Sciences of 362 dark-skinned patients with photodermatoses reported systemic DIP to be 1.9 % (7 patients); seven different culprit drugs were identified (ibuprofen, hydrochlorothiazide, torsemide, ornidazole, doxycycline, naproxen and atorvastatin) of which five (ibuprofen, hydrochlorothiazide, doxycycline, naproxen and atorvastatin) were also taken by the 475 participants, (Wadhwani et al., 2013).

Chaabane *et al*. (2013) reported that DIP is the third most common diagnosis in a study of 118 patients presenting with cutaneous drug-induced adverse effects. Nineteen cases of photosensitisation were identified with cardiovascular drugs (thiazide diuretics and amiodarone) the most common culprit. NSAIDs, fluoroquinolones, tetracyclines, lipid-lowering fenofibrate and neuroleptics were also identified as culprit drugs (Chaabane et al., 2013).

Nakao *et al.* (2017) reviewed an adverse drug event database and found 330 reports of DIP amongst 430,587 reports submitted (0.77%). This lower rate of DIP prevalence compared with studies which report on patients attending outpatient departments may be due to the nature of adverse incident reporting with DIP potentially not reported due to constraints on clinicians' time and awareness both of DIP and reporting systems (Nakao et al., 2017).

A retrospective report from the Dundee Photobiology Unit (Ninewells Hospital, Scotland), found DIP prevalence rate of 4% amongst patients that bad been refereed for phototesting due to suspected photosensitivity (Dawe and Ibbotson, 2014). The first project of this thesis which was a retrospective review of patients referred for photoinvestigation, found the prevalence rate of 5.44% (Alrashidi et al., 2020).

As it can be seen, a wide range of DIP rates have been reported ranging from as low as 1.9% to 14.5% This wide range of results may be partially explained by older reports including drugs that have since been discontinued (Khoo et al., 1996) with more recent publications, with a similar culprit drug profile, reporting prevalence rates somewhat more similar to the data presented in this thesis, for example, the DIP prevalence of 1.9 % by Wadhwani *et al* (2013) versus our 5.4%.

As authors have highlighted it is difficult to compare across different healthcare systems due to different prescribing practices (Wong and Khoo, 2005). Further, comparison between countries may also be affected by factors such as phototype which has been suggested to impact DIP rates (Nakamura et al., 2014) and the challenges of making assumptions about phototype based on country have been highlighted (Stratigos et al., 2003).

Prospective evaluations of the community-based drug photosensitivity within the UK are lacking and the findings presented here represent the first investigation of the community DIP rate and key culprit drugs.

4.10.2 The potential photosensitisers

4.10.2.1 Anti-hypertensives

By far the greatest number of participants (19.7%) were taking drugs broadly grouped into the anti-hypertensive category. This is unsurprising given recent estimates of the prevalence of the cardiovascular disease in the population at 21.3% (Hinton et al., 2018). A study of management of hypertension in 21,024 patients diagnosed in UK general practice found that diuretics and beta-blockers made up 32% and 22% respectively of first-line treatment for hypertension (Walley et al., 2003). A more recent study found that of 1,275,174 patients diagnosed in UK general practice, 13% were taking ACE inhibitors, 11.7% CCBs, 8,9% beta-blockers, 7.75% thiazide diuretics and 4.9% angiotensin receptor blocker (ARBs) (Hinton et al., 2018); this compares to our results (n= 475), where the rates were lower at 4.8%, 5%, 3.9%, 1.5% and 2.2% respectively.

The higher prescribing rates reported for these anti-hypertensive drugs by Hinton *et al*. (2018) is significant in terms of DIP as 44% of our anti-hypertensive drugs were potential photosensitisers with the majority of potential photosensitisers in the subclasses ACEs inhibitors (50%), ARBs (80%), CCBs (66%) and thiazide diuretic agents (100%). Using the figures presented by Hinton *et al.* (2018) this would represent, for example, 82,886 patients seen in general practice potentially taking photosensitising ACEs inhibitors. Thus, the numbers of patients at risk of possible DIP may be greater in the community due to the higher prescribing rates than we observed amongst our participants.

Amongst the n=10 group, amlodipine-associated DIP was identified in two cases representing 3.9% of the 51 participants who were taking this particular calcium channel blocker (Table 4-4). Eight cases of amlodipine associated with photodistributed telangiectasia were reviewed Bakkour *et al*. (2013) with the further case reported in 2017 (Bakkour et al., 2013, Rojas Mora et al., 2017). Onset typically occurs within one year of commencing the medication with remission reported as occurring after at least three months of withdrawal (Ioulios et al., 2003). It is interesting to note that in two of our participants, symptom onsets occurred two years after commencing amlodipine and simvastatin or amlodipine and citalopram. It is possible that the dosage of the participant's medication was increased at some point closer to the onset of their symptoms. The questionnaire was not designed to capture that information; however, such detail would be identified as part of a full photoinvestigation.

Diltiazem was suspected in one of the ten probable cases; thus, probable diltiazem DIP occurred in 20% (five were taking this medication) amongst the 475 participants. However, this participant was taking a further six potential photosensitising agents; therefore, phototesting would be recommended to establish greater confidence for a causal relationship. The first project of this study found only a single case of DIP attributable to diltiazem following photoinvestigation. Diltiazem has a long history of association with DIP; early report describe photosensitive erythroderma (Young et al., 1990, Wittal et al., 1992). However, the majority of case reports describe a slate grey reticulated photodistributed hyperpigmentation (Boyer et al., 2003a, Jaka et al., 2011, Kubo et al., 2010, Scherschun et al., 2001). The action spectrum of diltiazem has been reported as both UVA (O'Reilly et al., 1999) and UVB (Saladi et al., 2006, Desai et al., 2010). The duration between commencement of medication and onset of DIP has been reported to range from 6-8 months (Jaka et al., 2011, Scherschun et al., 2001).

Irbesartan DIP is rarely reported; Viola *et al.* (2015) reviewed the World Health Organization Global Individual Case Safety Report database, VigiBase®, and found 46 reports of "photosensitivity" and one of "solar dermatitis" for irbesartan between 1999 and 2014. Of these 47 reports, three were identified as "well documented" with participants taking no other known photosensitisers (Viola et al., 2015). Nakao *et al*. (2017) reviewed the Japanese adverse drug event report database and noted that for the combination of irbesartan and amlodipine; 96 adverse events were reported between 2004 and 2016, of which one was classified as photosensitivity (Nakao et al., 2017). Photoinvestigation as reported in part one of this study did not find any cases of irbesartan-associated DIP.

The questionnaire identified six participants amongst the 475 who were taking irbesartan and of these, a "probable DIP" was found in only one case (16.7%). However, it must be noted that this participant was taking a further five known potential photosensitisers: azathioprine, diltiazem, quinine sulphate, indapamide and simvastatin.

Indapamide is a thiazide-like diuretic and was taken by four of the 475 participants; it was found to temporally correlate with an abnormal sunlight response in one out of the ten (10%) probable cases of DIP participant. However, this participant was taking a further five potential photosensitising agents therefore phototesting would be required to establish greater confidence for a causal relationship.

Very few reports of indapamide-associated DIP exist (Rutherford and Sinclair, 2007); however, Jensen *et al.* (2008) have reported an increased risk of malignant melanoma in indapamide users (Jensen et al., 2008).

4.10.2.2 Anti-depressants

The majority (80%) of antidepressant taken by the n =475 participants were potential photosensitising agents. Antidepressant prescribing levels within the UK reported by Marsden *et al*. (2019) reveal 16.6% of the UK population had one or more antidepressant prescriptions between 2017 and 2018 (Marsden et al., 2019). Of the 475 participants within our study taking antidepressant was lower (6.8%). Potentially photosensitising SSRIs were the antidepressant taken by the majority of participants (52%). The predominance of SSRIs in antidepressant prescribing has been previously reported (Bauer et al., 2008); however, they report slightly higher levels of SNRIs prescribing than tricyclic antidepressants, whilst in this study, the findings were reversed (SNRI: 6% and TCA 40.6%). This difference in prescribing patterns may be significant since all the TCAs taken by our participants were potential photosensitisers.

In our participants (n=10), citalopram was a possible culprit in two (8.7%) of 23 participants taking this SSRI whilst sertraline was suspected in a further two of 18 cases (11%) of all 1,416 drugs taken by 475 participants (Table 4-4). There are relatively few reports of photosensitivity associated with SSRIs; citalopram has been associated clinically with photodistributed hyperpigmentation and drug-induced SLCE was reported in one case (Röhrs et al., 2012, I˚ nalöz et al., 2001), and a photoallergic reaction has been reported with sertraline (Lin et al., 2009).

The first study included in this thesis found that in patients who underwent photoinvestigation, SSRIs accounted for only 4.1% of cases, two due to sertraline and one due to citalopram.

Few reports give any indication of the prevalence of DIP associated with these drugs; Korzeniowska *et al*. (2019) report six of their 356 patients were taking citalopram and 11 were taking sertraline but they found no cases of DIP. As with many of the drugs identified as possible culprit photosensitisers, prescribing levels are high (90,406 and 72,246 for citalopram and sertraline respectively, so that even rare adverse reactions may affect many individuals .(Business Services Authority 2020)

4.10.2.3 Proton pump inhibitors

For the 475 participants in this study, the prevalence of PPIs was 9.3% (132 of 1416 drugs) of which 77% (102 of 132 PPI's) were known potential photosensitisers (Table 4-4); therefore, photosensitising PPIs represented 7.2% (102 of 1416) of the 475 participants, rising to 12.2% amongst the 112 subset taking a potential photosensitiser and reporting atypical sunlight responses . Omeprazole was the main culprit drug, being taken by 6.8% of all 475 participants (Table 4-4). The numbers of participants taking PPIs within our study was very similar to the estimate of national prescribing levels, where a point prevalence of 7.7% in 2014 has been reported (Othman et al., 2016). The relatively high prescribing rate combined with greater prescribing of PPIs associate with photosensitivity (i.e. esomeprazole, omeprazole and pantoprazole) increases the likelihood of DIP being observed. Considering the ten participants identified as probable DIP, five participants were taking the potentially photosensitising omeprazole, which represents 5.1% of those taking this drug (n = 97). The first presented study, 12 cases were attributable to PPI (9.8%), of which eight were associated with omeprazole (Alrashidi et al., 2020).

PPIs are most commonly associated with drug-induced SCLE: esomeprazole (Alcántara-González et al., 2011, Gliem et al., 2017b), lansoprazole (Bracke et al., 2005a, Panting, 2009), report five cases of cutaneous lupus erythematosus: lansoprazole/omeprazole/pantoprazole (Dam, 2008) and pantoprazole and esomeprazole (Almebayadh et al., 2013).

Sandholt *et al*. (2014) reviewed the medical records of 727 patients referred to a hospital Dermatology and Allergy Department in Denmark between 1994 and 2013; they identified 121 patients where drugs were potentially causing, or aggravating, lupus erythematosus, of which 24 were PPIs, and five cases were linked specifically to omeprazole (Sandholdt et al., 2014). A report from the same cohort of patients identified a further case of drug-induced SCLE associated with omeprazole, bringing the total to six over 19 years (Dam and Bygum, 2008). Grönhagen *et al*. (2012) found that in a population-based case-controlled study of 234 SCLE in Sweden, the odds ratio of developing a photosensitivity reaction after taking PPIs was 2.9 (Grönhagen et al., 2012). A review of the literature was unable to find any reports of omeprazole-associated DIP that were not associated with lupus. However, the omeprazole patient information leaflet listed photosensitivity as a rare side effect.

Omeprazole has been available for clinical use since 1988 and is widely prescribed, for example, 164,369 prescriptions (new and/or repeat) were issued by NHS England in December 2019 (Business Services Authority 2020). One plausible reason for the high number of omeprazole-associated cases, therefore, might be the increased use in the current decade. Given the high prescribing levels our finding of DIP may therefore be clinically relevant and these results should be disseminated to the wider clinical community (Alrashidi et al., 2020).

4.10.2.4 Cholesterol-lowering agents

Amongst the 475 participants, 108 (7.63%) were taking cholesterol-lowering agents. Hawkes *et al.*(2017) has suggested that by following NICE guidance, as many as 37% of all adults aged 30-84 would be recommended statin therapy (Hawkes, 2017), while Hinton *et al.* (2018) reported 12.8% of 1,275,174 patients attending general practice were taking statins (Hinton et al., 2018), a figure higher than that observed in our participants.

Amongst our probable DIP participants (n= 10), the cholesterol-lowering agents, atorvastatin and simvastatin, were suspect drugs in three participants representing 6.4% of the 47 individuals within the 475 participants taking cholesterol lowering agents (Table 4-4); While earlier photoinvestigation results had shown that statins account for six (5.7%) DIP cases (two cases with atorvastatin and five cases with simvastatin).

Atorvastatin is the statin recommended in the NICE clinical guideline CG181 (Cardiovascular disease: risk assessment and reduction including lipid modification) and was prescribed 235,048 times in the UK by the NHS in December 2019 while simvastatin was prescribed on 100,209 occasions (Business Services Authority 2020).

Korzeniowska *et al*. (2019), in a study from Poland, also note more frequent prescribing of atorvastatin (191/356) than simvastatin (23/356), reporting two cases of DIP for both atorvastatin (1.04%) and simvastatin (8.7%) in a cohort of 356 older (65-98 years) patients (Korzeniowska et al., 2019). Wong *et al.* (2019) reviewed 104,372 adverse cutaneous drug reactions reported in Singapore between 2006 and 2015 (Wong et al., 2019). They reported 113 incidents of photosensitivity involving 123-suspected drugs of which five were simvastatin. Simvastatin appears to be more frequently associated with photosensitivity than atorvastatin; however, the over the double prescribing rate of atorvastatin in NHS England may results in broadly similar number of DIP patients being seen (NHS Business Service Authority 2020).

4.10.2.5 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are widely prescribed accounting for over 15 million prescriptions in 2014 (Davis and Robson, 2016) and they have been reported to account for 29.6% of hospital admissions due to adverse drug reactions (Pirmohamed et al., 2004). A total number of 122 (8.6%) participants in our study were taking eight different types of NSAIDs, of which five, representing 51.6% of all NSAIDS taken, were potential photosensitising agents (62.5%; Table 4-4).

Five NSAIDs were associated with photosensitivity: ibuprofen (taken by 28 people), diclofenac (taken by four people), mefenamic acid and sulindac (taken by two people each) and naproxen (taken by 27 people; Table 4-4). Naproxen was identified as the culprit photosensitiser in a single participant of the ten-probable case of DIP. The participant was taking no other known photosensitising agents. Twenty-seven of 122 possible DIP respondents were taking naproxen; thus naproxen-associated probable DIP occurred at a rate of 3.7%. Naproxen photosensitivity is well documented, with 29 cases of pseudoporphyria (Farr et al., 1985, Levy et al., 1990, Lützow-Holm, 1991, Maerker et al., 2001, Rivers and Barnetson, 1989, Suarez et al., 1990, Stenberg, 1990) and photodistributed erythema multiforme and lichenoid photosensitivity have been described in 2 cases (Gutiérrez-González et al., 2011).

As has photosensitisation (Shelley et al., 1986) and erythema (Diffey et al., 1983). Nakao *et al*. (2017) analysed DIP reports submitted to Japanese Adverse Drug Event Report database and found 15/330 cases of NSAID-associated DIP but none involving naproxen (Nakao et al., 2017). Similarly, Korzeniowska *et al*. (2019) reported that of 61 patients using naproxen, no cases of photosensitivity were observed (Korzeniowska et al., 2019).

4.10.2.6 Chemotherapeutic agents

Twenty-five participants were taking methotrexate representing 1.76% of all 1,416 drugs taken (Table 4-4). Of these 25 participants, the questionnaire identified one case as a probable DIP (4%); however, the subject was also taking omeprazole and sertraline, hence photoinvestigation would be required to confirm the culprit photosensitiser.

Methotrexate photosensitivity has been found in a case report of a young child who developed erythema and vesicles following methotrexate treatment and light exposure (Fernández et al., 2012). Roenigk *et al.* (1969) reported photosensitivity in 5% of 204 patients receiving methotrexate to treat psoriasis (Roenigk et al., 1969).

There have been several reports of a phenomenon described as false photosensitivity where methotrexate reactivates a UVB or radiation-induced injury that occurred previously (Thami et al., 2002, Khan et al., 2000, Neiman and Fye, 1985, Möller, 1969). It has also been suggested that methotrexate can cause photosensitivity when used in combination with other drugs such as voriconazole (van Hasselt et al., 2013).

4.10.2.7 Anti-diabetic agents

Fifty-four participants were taking anti-diabetic agents representing 3.8% of all 1,416 drugs taken by 475 participants (Table 4-4). Although nine different anti-diabetic drugs were taken, the majority of participants were taking metformin (41 participants; 75.9%) and only metformin was associated with photosensitivity amongst our participants. Metformin was identified as a potential culprit drug in a single participant of the ten probable DIP cases and this subject was taking metformin as their only potential photosensitising agent at the time of onset of symptoms. This reflects national patterns of prescribing that have reported 73% initiating treatment for type 2 diabetes with metformin (Wilkinson et al., 2018).

There have been few reports of metformin-induced photosensitivity; Kastalli *et al*. (2009) reported three cases of metformin-induced photosensitivity with symptoms described as eczematous or erythematous lesions occurring between 22 days and four years after commencing the medication (Kastalli et al., 2009). Korzeniowska *et al.* (2019) in their survey of 356 patients attending outpatient departments reported an adverse photosensitivity reaction (erythema) in two of 95 patients taking metformin (Korzeniowska et al., 2019). They additionally highlight that metformin is not widely regarded as a photosensitising drug and conclude that this increases the potential for cases of photosensitivity to be missed. Metformin became available in the UK in 1958 and worldwide, is reportedly the most prescribed glucose-lowering medication (Bailey, 2017); therefore, even a low incidence of photosensitivity may affect many patients.

4.10.2.8 Anti-malarial

The anti-malarial drugs, quinine and hydroxychloroquine were taken by 12 (0.85%) participants of all 1,416 drugs taken by 475 participants (Table 4-4). Despite the relatively low numbers taking these drugs, probable DIP was identified in one case of quinine and one case of hydroxychloroquine representing 33.3% and 11.1% of participants taking these medications. The potential photosensitivity activity of quinine has been known for over 150 years (Spikes, 1998) with over 27 clinical publications recently reviewed by Hofmann *et al*. (2020) (Hofmann et al., 2020). The most commonly identified drug associated with DIP by photoinvestigation in our first study was quinine, which represented 11.5%; however, the questionnaire identified only one probable case of quinine-induced photosensitivity and this participant was taking five other potential photosensitising agents.

Hydroxychloroquine has been used since the 1960s (Gabourel, 1963); however, reports of DIP are uncommon, with only seven cases reported in the literature (Metayer et al., 2001, Callaly et al., 2008, Lisi et al., 2004, van Weelden et al., 1982). The questionnaire identified a single participant with hydroxychloroquine-induced probable DIP; this participant was also taking azathioprine, another known photosensitising agent. Prescribing levels of quinine (sulphate and bisulphate) are more than double that of hydroxychloroquine (14,703 and 5885, respectively) (Business Services Authority 2020). A search conducted of the WHO global database of individual case safety reports, VigiBase® (Lindquist 2008), using VigiAccess® showed 62 reports of photosensitivity for quinine and 166 for hydroxychloroquine (Lindquist, 2008).

Wong *et al*. (2019) reviewed 104,372 adverse cutaneous drug reactions reported in Singapore between 2006 and 2015. They reported 113 incidents of photosensitivity involving 123-suspected drugs of which two were attributable to hydroxychloroquine. Although these databases give an indication of the prevalence of side effects, no evaluation of the quality of the attribution was made; for example, it was not known if the patients were taking one or many potential photosensitisers, whether phototesting was carried out or whether symptoms resolved on withdrawal of the drug.

4.10.2.9 Immunomodulators

Immunomodulatory drugs made up a relatively small proportion (0.78%) of the drugs taken by the n=475 group. Azathioprine was a suspected culprit in two participants with probable DIP (n=10), both taking more than one potential photosensitiser. Thus, two of the three participants taking azathioprine and 18% of the 11 participants taking immunomodulatory drugs (Table 4-4), were identified as a probable DIP.

In the first study contained within this thesis, azathioprine was identified in a single case amongst patients that had undergone photoinvestigation within the Photobiology Unit at Salford Royal Hospital (Alrashidi et al., 2020). Azathioprine is a photosensitiser that produces reactive oxygen species on interaction with light and is reported to reduce the erythemal threshold to UVA (Hofbauer et al., 2012, Perrett et al., 2008) and so increasing the risk of skin cancer in immunosuppressed patients (Jiyad et al., 2016). Reports of incidence of photosensitivity could not be found; however, the British National Formulary (2020) describe photosensitivity and neoplasm as “rare or very rare” clinical events and similarly the summary of product characteristics describes the incidence of photosensitivity as “unknown” (Electronic Medicines Compendium 2019).

A search of World Health Organisation adverse drug event database, VigiBase® (Lindquist 2008) using VigiAccess®, showed 101 reports of photosensitivity (Lindquist, 2008). As azathioprine is known to increase the risk of SCC development, it is important that patients who identify themselves as having redness and/or a burning reaction that they do not think is normal sunburn and is more severe than that observed in their family and friends, are properly monitored by a dermatologist.

4.10.3 Effectiveness of sun protection measures

The majority of participants, both those categorised as 'probable DIP' (n=10) and 'possible DIP' (n=112), reported a worsening of their symptoms in the summer and on sunny days. These observations might be expected as UVR levels are greater in the summer months (Sliney and Wengraitis, 2006, Diffey, 2018) and the absence of cloud cover (Andersen et al., 2010); thus, conditions induced or exacerbated by UVR might be expected to worsen.

Amongst the participants where there was no temporal relationship between redness/burning and medication, using sunscreen eased symptoms for the majority. However, for the patients with probable DIP, the benefits of sunscreen use were less clear, with 50% reporting no effect on their symptoms. The questionnaire design was not formulated to collect detailed information about the type of sunscreen that had been used. For example, a high SPF/ low UVA sunscreen could be less effective than a broad-spectrum one for patients taking drugs that absorb in the UVA range, and this may partly account for the larger number of patients reporting no effect of sunscreen.

Sunscreen application is known to be suboptimal and with the increased sensitivity associated with DIP and other photosensitivity disorders, the correct application would be essential for maximum benefit (Petersen and Wulf, 2014, Jovanovic et al., 2017). For patients diagnosed with a photosensitivity disorder (described in Chapter One of this thesis), education in correct sunscreen application technique should include advice on the importance of a double application (Heerfordt et al., 2018) and the thickness of that application (Teramura et al., 2012).

A Danish study reported that there had been an improvement in the SPF factor chosen by the public rising from SPF5 in 1997 to SPF 20 in 2016 (Heerfordt et al., 2017); however, this is considerably lower than would be recommended by clinical photobiologists, the Photobiology Unit at Salford Royal Hospital recommends SPF50+ for photosensitive patients. Although SPF measures protection against UVB, it does not provide information about how much UVA protection is provided. Many sunscreens can provide good UVB protection but insufficient UVA protection (Marionnet et al., 2015). As discussed in part one study, DIP is associated with increased sensitivity to UVA therefore even though participants stated they were using sunscreen they might be choosing a product that does not offer adequate UVA protection.

The majority (80 %). of participants reported a benefit from clothing, for example, their symptoms were reduced when covered with clothing before sun exposure. Clothing can offer excellent protection (Ghazi et al., 2010, Morison, 2003, Broeshart et al., 2003), but the choice of clothing is critical and may not be widely known amongst the general public. Gambichler *et al.* (2002) noted that one-third of summer clothing provided a UVR protection factor of less than 15 and Adam (1998) reported a standard t-shirt might only offer a protection factor of 7 (Gambichler et al., 2002, Adam, 1998).

However, the protection afforded by clothing can be improved by careful selection. Wang *et al*. (2001) reported the effects of laundering on a standard t-shirt and noted the use of detergents and UVR absorbers increased the UVR protection factor by as much as 400% (Wang et al., 2001); similarly, Gamblichler *et al.* (2001) noted that darker colours afforded better protection than lighter ones (Gambichler et al., 2001).

To aid in the selection of UVR protection factor' (UPF) clothing, a European standard has now been established that states that clothing may be labelled UVP 40+ if having a UVR protection factor above 40 and transmitting less than 5% of UVA (Gambichler et al., 2006). The majority of participants benefitted from physical photoprotective measures; however, it would be interesting to further investigate sunscreen and clothing choices in further detail particularly amongst participants who felt they were of no benefit.

4.10.4 Strengths and weaknesses of the study

Analysis and interpretation of data from the questionnaire allowed the identification of 10 cases of "probable DIP". These individuals would require a full photoinvestigation to confirm the suspected diagnosis. Further, the questionnaire highlighted how many participants were taking potential photosensitisers and were thus at risk of DIP. The questionnaire was a quick and easy tool to use and with further validation could be used to rapidly screen participants for potential DIP.

The response rate to the study was 53.8%. Although this value was perhaps lower than might have been hoped for, it is broadly similar to previous response rates reported by a questionnaire-based study at the Photobiology Unit at Salford Royal Hospital (Jong et al., 2008).

The issue of lower response rates in epidemiological-based studies has been highlighted. Lower response rates may be associated with non-participation bias potentially leading to inaccurate results. A range of reasons have been suggested including request overload, perceived lack of relevance and time commitment required (Galea and Tracy, 2007, Harrison et al., 2020, Flink et al., 2019, Arfken and Balon, 2011).

The mean age of the participants was 64 (range 40-94) for the 475 groups and 62.1 (range 45-88) for the 112 participants reflecting the association between age and the tendency to be taking some form of medication. Females made up 63.6% of our respondents, a figure very similar to that reported by Korzeniowska *et al.* (2019) who reported 63% female respondents (Korzeniowska et al., 2019). This predominance of women raises the potential for gender bias. It has been reported that women are more likely to receive prescriptions of antibiotics (Ramos et al., 2015, Schröder et al., 2016), whilst men are more likely to receive an opioid prescription (Preciado et al., 2020); similarly, an American study also reported that women are significantly more likely to be taking several medicines (Manteuffel et al., 2014). Although historically women are underrepresented in clinical trials (Bartlett et al., 2005), this may be related to their not having been offered the opportunity to participate. A recent study inviting the public to join a recruitment registry found female participation to be higher (Kannan et al., 2019). Similarly, Ramos *et al*. (2015) reported men were less likely to take part in epidemiological studies (Ramos et al., 2015). In this study 112 felt they had a redness/burning feeling that was not sunburn and was worse than family and friends, yet a temporal relationship to medication could only be found in ten participants.

The question, therefore, arises 'what could be causing this perceived abnormal response?'

It is possible that some of the participants had an undiagnosed photosensitivity disorder. Polymorphic light eruption with a prevalence of 17.3% reported for the UK (Rhodes et al., 2010), thus one might expect in 19 cases amongst the 112 participants, although typically PLE is described as a papular vesicular rash rather than burning/redness (Ling et al., 2003). Other possible photosensitivity disorders include chronic actinic dermatitis, typically more common in older and male populations (Ferguson, 2006), although exceptions have been reported (Ogboli and Rhodes, 2000).

Solar urticaria is associated with rapid onset erythema that resolves within hours (Beattie, 2006), which participants might describe as a burning redness. One participant reported a worsening of their symptoms when using sunscreen, which must also raise the possibility of a contact/photocontact allergic reaction. It is interesting to note that the majority of this subset also reported a worsening of their symptoms in the summer and on sunny days, responses typical of photosensitivity disorders such as polymorphic light eruption (Ling et al., 2003) or SLE (Hasan et al., 2004).

A further confounding factor amongst this group could be recall bias (Spencer et al., 2017). We were asking participants to recall drug start dates from a considerable time ago, and it is possible that recall was not always accurate.

In this study, an association was found between Fitzpatrick skin types and perceived abnormal responses, with skin type I more likely to report a response that they felt was not normal sunburn than skin type IV amongst the possible DIP subset. This may have been simply due to confusion between the perception of a "normal" and a "not normal" sunburn response; however, it is also possible that these participants had incorrectly recalled medication start dates and were indeed taking potential photosensitisers. The relationship between DIP and skin phototype has not been widely examined. Kerr and Lim (2007) found no significant difference between DIP rates in African Americans and Caucasians (Kerr and Lim, 2007); however, a follow-up study in 2014 found DIP rates to be significantly higher in Caucasians (Nakamura et al., 2014). However, they do state that in these retrospective studies only broad racial categories were available and that African Americans and Caucasians can have overlapping phototypes.

Higher rates of DIP were reported from Norway (8%) (Selvaag, 1997) than the UK (Dawe and Ibbotson, 2014) and Greece (4.8%; (Stratigos et al., 2003) although they caution against assumptions of skin type based on country noting that although Greeks are assumed to have darker skin a substantial number have light skin (Types II & III).

Three reports from India have broadly similar rates (2%) (Patel and Marfatia, 2008), 3.8% (Saha et al., 2012) and 1.9% (Wadhwani et al., 2013). Only the last study gives phototype data noting all participants were skin types IV-VI (Wadhwani et al., 2013). The highest rates of DIP were reported from Singapore (11.3%) (Khoo et al., 1996) and 13% (Wong and Khoo, 2005); however, no indication of phototype was given in the former study and the latter study lists only ethnicities which it does not break down for the DIP patients. Maresca *et al.* (2006) note that pheomelanin, typically present in higher abundance in skin types I and II, is less effective at scavenging free radicals than eumelanin, present in darker phototypes (Maresca et al., 2006); thus potential photosensitisers that generate reactive oxygen species may have a greater impact on lighter skins. However, Schiener *et al.* (2001) found no correlation between skin phototype and minimum phototoxic dose following psoralen bath exposure (Schiener et al., 2001). It would be of interest in any future work to explore the relationship between skin phototype and DIP.

4.10.5 Further outcomes

A further aim of this study was to determine the key characteristics of participants identified as probable cases of DIP in order to identify factors that may predict which patients are at risk of DIP; however, this was not possible due to low number of probable cases of DIP identified and the fact that the majority were taking more than one potential photosensitiser that temporarily correlated with their symptoms.

Results from this project did highlight that not everyone taking a potential photosensitiser will develop symptoms of photosensitivity. There may be several reasons for this. Drug dose and cumulative treatment time may have an impact, for example, Sheu *et al*. (2015) reported increased risk of voriconazole phototoxicity in children treated for 6 months or longer (Sheu et al 2015).

Photosensitivity reactions and photodamage associated with the phototoxic response may increase the risk of skin cancer development (Stern, 1998). Voriconazole phototoxicity has been associated with squamous cell carcinoma (SCC) development (McCarthy et al., 2007, Cowen et al., 2010) with cumulative treatment time and dose both factors predictors of this endpoint (Singer et al., 2012).

The risk of DIP due to combination of drugs has not been widely examined, although case studies of phototoxic reaction due to combined drugs gave been reported (Amelot et al., 2014, Richarz et al., 2017). The photocarcinogenic potential of drug combinations, for example, Jensen *et al.* (2008) reported an increased risk of developing squamous cell carcinoma and malignant melanoma following combined amiloride and hydrochlorothiazide (Jensen et al., 2008). Further, *in vitro* studies have suggested a combination of the tyrosine kinase inhibitor anti-cancer drugs gefitinib and imatinib might increase the risk of retinal phototoxicity when combined with ciprofloxacin (Mealey et al., 2014).

Pre-existing conditions can also increase the risk of a phototoxic response. For example, Tolland *et al*. (2012) reported that ciprofloxacin phototoxicity was increased in patients with pre-existing cystic fibrosis (Tolland et al., 2012). Even the time at which a medicine is taken may affect the patients reporting of photosensitivity side effects. A study by Lowe *et al.* (1994) found that evening dosing with quinolone antimicrobial lomefloxacin was associated with reduced UVR sensitivity compared to morning dosing (Lowe et al., 1994).

The potential impact of skin type was highlighted above in the lower incidence of DIP reported amongst African Americans versus Caucasians, although it should be noted that this classification was based on ethnicity rather than phototype (Nakamura et al., 2014). Similarly, Kligman *et a.l*. (1982) examined photosensitivity following benoxaprofen in healthy volunteers and noted a greater risk in skin types I & II (Kligman and Kaidbey, 1982).

The benefits of good sun protection practices in preventing photosensitivity symptoms developing have been reported (Grose and Ramien, 2019, Medeiros and Lim, 2010, Korzeniowska et al., 2019), It is possible that a proportion of the participants taking potential photosensitising drugs did not report atypical responses due to sunlight as they were adequately photo protecting. Further study characterising the dose, time of dosing treatment, duration, drug combinations, pre-existing conditions, type and usage of photoprotective measures may help in predication the population at risk of developing DIP.

4.11 Conclusion

The data analysis suggested that the community-based prevalence of probable cases of DIP was 2.1%, where PPIs, ACEs, ARBs and statins were the most common culprit class of medications. Statins were not among the previously most commonly reported culprits. This potentially reflecting an increase in the prescription rate of these medications and their requirement to treat other age-related health conditions. The questionnaire allowed the identification of ten ‘probable’ cases of DIP; however, further phototesting would be required to confirm these results, which highlights the importance of this comprehensive clinical photobiology testing service. This initial use of the questionnaire suggests it has potential as a tool to quickly screen patients for possible DIP, although further validation would be required to address some of the issues highlighted.

Chapter 5: Conclusion

Drug-induced photosensitivity (DIP) is a potential side effect of medications that can easily be undiagnosed or under-reported, leading to an underestimation of its prevalence. Additionally, the prevalence of DIP varies with different drug classes and in individuals' responses to the same medicine. Several factors can affect the prevalence of DIP; as a result, estimation of the prevalence is not a straight forward process. In the UK the prevalence of DIP has been previously reported to be 4% (Dawe and Ibbotson, 2014). Additionally, with the constant development of novel medications, there is always the possibility that DIP will be an undesirable or unappreciated side effect. Thus, a better understanding of potential current culprit drugs that may induce DIP, the diagnostic characteristics of the reaction and the impact of DIP on the QoL are essential.

My thesis has studied several factors of DIP, namely the prevalence and clinical characteristics of the reaction using a retrospective data set of photosensitive patients diagnosed in the Photobiology Unit at Salford Royal Teaching Hospital (Salford Royal NHS Foundation Trust; 2000-2016), and data collected from a wider community (outpatients department at Salford Royal Teaching Hospital; 2018-2019).

5.1 Study 1 (Chapter 3): Prevalence of drug-induced photosensitivity in patients' undergoing photoinvestigation

The study design was a case series of patients who were diagnosed at the Photobiology Unit (The Dermatology Centre, Salford Royal NHS Foundation Trust, UK) from 2000 to 2016. Study aims were first, estimation of DIP prevalence amongst patients who were diagnosed with photosensitivity conditions. Second, identification of culprit drugs associated with DIP amongst this population and exploring for any emerging potential photosensitisers. Third, identifying the clinical and photobiological characteristics of these patients. Finally, studying the effects of DIP on the patient's quality of life.

The key findings were that the prevalence of DIP amongst patients referred for photoinvestigation was 5.4%; 51 culprit drugs accounted for the cases of DIP, with four drug categories making up 44% of cases. These four categories were antimalarial (mainly quinine), thiazide diuretics (mainly bendroflumethiazide), antifungal agents (mainly voriconazole) and proton pump inhibitors (PPI; mainly omeprazole).

Positive provocation test results to broadband UVA was the most common finding on photoinvestigation. Abnormal MEDs following monochromator testing to narrowband UVA was reported in 85.7% of quinine-associated DIP, 20% of thiazide diuretic-associated DIP, 41.6% of antifungal-associated DIP and 27.3% of PPI-associated DIP. In the majority of the cases (53.3%), the symptoms were manifested during the months of spring-summer, while 37.7% reported that they had symptoms throughout the year.

DLQI results showed that over the week before testing, QoL was moderately impaired in 24% of those surveyed, very largely impaired in 22%, and extremely largely impaired in 3.7%. When asked to review the impact over the last year, the impact on QoL increased (moderate impairment 41%, were very large impairment 31% and extremely large impairment in 17.2%).

This study is significant because it evidences the contribution of DIP diagnosis to photosensitivity disorders. Furthermore, a novel finding that DIP due to PPIs (mainly omeprazole) presented as a photosensitive eczematous reaction and sunburn-like reactions. Rather than drug-induced SCLE, as that has been described previously in the literature; lansoprazole (Bracke et al., 2005a, Panting, 2009), lansoprazole, omeprazole and pantoprazole (Dam, 2008), pantoprazole and esomeprazole (Almebayadh et al., 2013) and omeprazole (Sandholdt et al., 2014, Dam and Bygum, 2008).

In addition, the study showed the importance of repeated provocation testing to broadband UVA as a diagnostic tool and that photosensitivity caused by quinine can be effectively diagnosed by monochromator testing to narrowband UVA. Additionally, this study showed that DIP has a significant impact on a patient's quality of life.

Limitations of this study included: its retrospective nature, which relied on clinical notes that had been collected at the time of the diagnosis. Patients were taking a complex range of medications and identifying the culprit drug was challenging. Absence of a definitive diagnostic test means the diagnosis of DIP should be regarded as probable rather than definite, particularly as retesting was not always performed, as travelling long-distance to the Photobiology Unit was an obstacle for many of the patients.

Interestingly, the data highlights a developing issue of DIP reactions occurring in patients where PPIs were the probable culprit drugs. These findings require further validation, potentially using collaborators in multiple centres to corroborate these findings.

This study indicated that DIP has a remarkably high impact on the patient's QoL, so clearly demonstrating the need to establish effective management strategies to diagnose the condition quickly and provide appropriate alternatives to aid its resolution and so reduce its impact on QoL.

5.2 Study 2 (Chapter 4): Prevalence of drug-induced photosensitivity in the outpatient's clinics community

The key aims of this study was to estimate the prevalence of DIP in the community. Further, to identify the demographic characteristics and the most common potential photosensitising. The questionnaire used was a modified version of a questionnaire that had been previously developed and used within the Photobiology Unit (The Dermatology Centre, University of Manchester, Salford Royal NHS Foundation Trust). The questionnaire was used to obtain information from participants attending the outpatients' clinic at Salford Royal Hospital to estimate the prevalence of DIP in the community. Participants were categorised into three groups: unlikely, possible, and probable case of DIP, with culprit medications and key demographic characteristics being identified.

The study identified ten probable cases of DIP (2.1%) who were taking 15 drugs that were identified as a potential photosensitiser including PPIs, ACIs, ARBs and statins. Interestingly, amongst all participants, 1416 different medicine were being taken of which a high number (50.4%) were potential photosensitising medications. It was also notable that 23.6% of participants reported that they felt they had an abnormal reaction to sun exposure, even though this did not appear to be linked to their medication.

The study provided an estimation of DIP prevalence in the outpatient clinics (community), which demonstrated that a questionnaire could potentially be used as a screening tool to identify the DIP in the clinic. Additionally, the results highlight photosensitivity as a potential issue amongst widely prescribed drugs such as PPIs.

There were potential issues of bias - particularly recall bias - as the participants were asked to recall medicine which had been taken, in some cases, as long as ten years ago.

Great effort goes into ensuring that the potential benefits of new medicines outweigh any potential side effects. Drugs development aims to avoid structures that are associated with phototoxicity such as aromatic ring-shaped planar molecules or conjugated double bonds containing nitrogen, sulphur or oxygen in the structure (Tamat and Moore, 1983). *In vitro* testing aims to screen out phototoxic drugs (Onoue et al., 2017, Kim et al., 2015) and clinical testing highlights potential side effects before a drug comes to market (Khandpur et al., 2017).

However, there are still new side effects that do not come to light until the drug is made widely available and the potential number of undiagnosed DIP may be considerable. For example, for the proton pump inhibitors: there are 46,887,724 adults (>19 years) patients registered at English GP practices (NHS, Digital 2020). The community-based questionnaire in this thesis found 7.2% participants were taking PPI's, which would represent approximately 3,375,916 individuals registered with English GP practices taking PPI's.

The result from the second project found that the percentage of participants taking omeprazole was 6.8% representing 3,188,365 individuals at potential risk of DIP. In addition, 5.1% of the questionnaire respondents taking omeprazole had probable DIP. In the English population taking omeprazole would represent 162,606 individuals potentially with undiagnosed DIP.

The reporting of adverse incidents is a two-step process requiring both the patient to recognise the drug adverse effects and the GP to have both the time and opportunity to report the event. Awareness and understanding of photosensitivity as a side effect may not be as good as might be expected; therefore, a formal system of proactively asking about photosensitivity may be desirable to ensure all photosensitive related side effects are captured.

5.3 Future work

A prospective study could be carried out in the future using a questionnaire amended using the feedback given by the participants. Potential changes could include:

- Widen the recruiting age to be above18 years in order to include all DIP in adults.
- Make the questions clearer either by collecting the responses via face to face interview or by trialling questions amongst focus groups to allow solutions to ambiguous questions to be identified.
- Create a list of medications for the patients to choose from and focus the questions on the most common medications that can cause DIP.
- Ideally, perform some cross checks with the participants GP to verify start and end dates for medication particularly where the suspected culprit drug was started many years ago.
- Validate the questionnaire so that it can be used as a quick tool for diagnoses of DIP at clinics. Validation is an essential next step to use the questionnaire as a diagnostic tool. Questionnaire validation would be a complicated process; however, the benefits of a validated screening tool would be considerable.
- A comprehensive validation study might initially involve recruiting participants at the time of starting their new prescription or using medical records to determine precise start dates and dosage. The questionnaire could then be used to identify those individuals who feel they have an atypical sunlight response with participants being invited to undergo photoinvestigation. Correlation of results with medicines being taken and the ruling out of other undiagnosed photosensitivity disorders could then be performed.
- Future studies combining the questionnaire and photoinvestigation should ideally be performed to confirm the diagnosis. The group of participants who reported an atypical sunburn response but could not recall taking any potential photosensitisers could also be further investigated.

References

AARSAND, A. K., BOMAN, H. & SANDBERG, S. 2009. Familial and sporadic porphyria cutanea tarda: characterization and diagnostic strategies. *Clinical chemistry,* 55**,** 795-803.

ABDEL-HAQ, N., SURAPANENI, V., SETH, D., PANSARE, M. & ASMAR, B. I. 2014. Voriconazole-Induced Photosensitivity in Children: A Case Report and Literature Review. *Global pediatric health,* 1**,** 2333794X14562230.

ÄBELÖ, A., ANDERSSON, T. B., ANTONSSON, M., NAUDOT, A. K., SKÅNBERG, I. & WEIDOLF, L. 2000. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metabolism and Disposition,* 28**,** 966-972.

ABREU-GERKE, L., GOERZ, G., MILLER, A. & RUZICKA, T. 2000. Acral necroses after therapy with quinine sulfate for calf cramps. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete,* 51**,** 332-335.

ADAM, J. 1998. Sun-protective clothing. *Journal of cutaneous medicine and surgery,* 3**,** 50-53.

ADDO, H., FERGUSON, J. & FRAIN-BELL, W. 1987. Thiazide-induced photosensitivity: a study of 33 subjects. *British Journal of Dermatology,* 116**,** 749-760.

AKAT, P. B. 2013. Severe photosensitivity reaction induced by topical diclofenac. *Indian journal of pharmacology,* 45**,** 408.

AL-KATHIRI, L. & AL-ASMAILI, A. 2016. Diclofenac-induced photo-onycholysis. *Oman medical journal,* 31**,** 65.

AL-KHENAIZAN, S., SCHECHTER, J. F. & SASSEVILLE, D. 1999. Pseudoporphyria induced by propionic acid derivatives. *Journal of cutaneous medicine and surgery,* 3**,** 162-166.

AL-NIAIMI, F. & CALUM, L. 2011. Mesalazine-induced photosensitivity. *European Journal of Dermatology,* 21**,** 105-106.

ALAM, M. 2004. Fitzpatrick's dermatology in general medicine. *Archives of Dermatology,* 140**,** 372-372.

ALCÁNTARA-GONZÁLEZ, J., TRUCHUELO-DÍEZ, M., GONZÁLEZ-GARCÍA, C. & JAÉN OLASOLO, P. 2011. Esomeprazole-induced subacute cutaneous lupus erythematosus. *Actas Dermo-Sifiliográficas (English Edition),* 102**,** 638-640.

ALFFENAAR, J., VAN ASSEN, S., DE MONCHY, J., UGES, D., KOSTERINK, J. & VAN DER WERF, T. 2010. Intravenous voriconazole after toxic oral administration. *Antimicrobial agents and chemotherapy,* 54**,** 2741-2742.

ALMEBAYADH, M., REGNIER-ROSENCHER, E., CARLOTTI, A., GOULVESTRE, C., LE GUERN, V., MOUTHON, L., AVRIL, M.-F. & DUPIN, N. 2013. Subacute cutaneous lupus erythematosus induced and exacerbated by proton pump inhibitors. *Dermatology,* 226**,** 119-123.

ALOISI, G. G., AMELIA, M., BARBAFINA, A., LATTERINI, L., ELISEI, F., DALL'ACQUA, F., VEDALDI, D., FACCIO, A. & VIOLA, G. 2007. DNA cleavage induced by photoexcited antimalarial drugs: a photophysical and photobiological study. *Photochemistry and photobiology,* 83**,** 664-674.

ALRASHIDI, A., RHODES, L. E., SHARIF, J. C., KREESHAN, F. C., FARRAR, M. D. & AHAD, T. 2020. Systemic drug photosensitivity—Culprits, impact and investigation in 122 patients. *Photodermatology, Photoimmunology & Photomedicine*.

ALVAREZ-FERNÁNDEZ, J., CASTAÑO-SUÁREZ, E., CORNEJO-NAVARRO, P., GÓMEZ DE LA FUENTE, E., ORTIZ DE FRUTOS, F. & IGLESIAS-DIEZ, L. 2000. Photosensitivity induced by oral itraconazole. *Journal of the European Academy of Dermatology and Venereology,* 14**,** 501-503.

ÁLVAREZ-PÉREZ, A., GÓMEZ-BERNAL, S., GUTIÉRREZ-GONZÁLEZ, E., RODRÍGUEZ-GRANADOS, M. T. & TORIBIO, J. 2012. Granuloma annulare photoinduced by paroxetine. *Photodermatology, photoimmunology & photomedicine,* 28**,** 47-49.

AMELOT, A., DUPOUY-CAMET, J. & JEANMOUGIN, M. 2014. Phototoxic reaction associated with M alarone (atovaquone/proguanil) antimalarial prophylaxis. *The Journal of dermatology,* 41**,** 346-348.

ANDERSEN, P. A., BULLER, D. B., WALKOSZ, B. J., SCOTT, M. D., MALOY, J. A., CUTTER, G. R. & DIGNAN, M. D. 2010. Environmental cues to UV radiation and personal sun protection in outdoor winter recreation. *Archives of dermatology,* 146**,** 1241-1247.

ANDERSON, C., LARSSON, L. & SKOGH, M. 1985. UVA photosensitivity in photosensitive bullous disease of chronic renal failure. *Photo-dermatology,* 2**,** 111-114.

ARFKEN, C. L. & BALON, R. 2011. Declining participation in research studies. *Psychotherapy and psychosomatics,* 80**,** 325-328.

ARRUE, I., ROSALES, B., ORTIZ, D. F. F. & VANACLOCHA, F. 2007. Photoaggravated eczema due to promethazine cream. *Actas dermo-sifiliograficas,* 98**,** 717.

AUFFRET, N., JANSSEN, F., CHEVALIER, P., GUILLEMAIN, R., AMREIN, C. & LE BELLER, C. Voriconazole photosensitivity: 7 cases. Annales de Dermatologie et de Venereologie, 2006. 330-332.

BAADSGAARD, O. 1986. Circulating and in situ lymphocyte subsets and Langerhans cells in patients with compositae oleoresin dermatitis and increased ultraviolet A sensitivity during treatment with azathioprine. *Journal of the American Academy of Dermatology,* 14**,** 577-581.

BACLE, A., BELAZ, S., POTIN, S. & GANGNEUX, J.-P. 2019. A case report of photodermatoses induced by the antifungal drug terbinafine. *European Journal of Hospital Pharmacy,* 26**,** 288-289.

BADIA, X., MASCARÓ, J. & LOZANO, R. 1999. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. The Cavide Research Group. *The British Journal of Dermatology,* 141**,** 698-702.

BAILEY, C. J. 2017. Metformin: historical overview. *Diabetologia,* 60**,** 1566-1576.

BAKER, K. 2016. Medicine statistics: GP prescribing by constituency, 2015. *House of Commons Library*.

BAKKOUR, W., HAYLETT, A. K., GIBBS, N. K., CHALMERS, R. J. & RHODES, L. E. 2013. Photodistributed telangiectasia induced by calcium channel blockers: case report and review of the literature. *Photodermatology, photoimmunology & photomedicine,* 29**,** 272-275.

BALER, G. 1976. Porphyria precipitated by hydroxychloroquine treatment of systemic lupus erythematosus. *Cutis,* 17**,** 96-98.

BALL, P. & TILLOTSON, G. 1995. Tolerability of fluoroquinolone antibiotics. *Drug safety,* 13**,** 343-358.

BAN, T. & LEHMANN, H. 1965. Skin pigmentation, a rare side effect of chlorpromazine. *Canadian Psychiatric Association Journal,* 10**,** 112-124.

BANGASH, H. K., PETRONIC-ROSIC, V., SETHI, A., ABRAMSOHN, E. & LINDAU, S. T. 2013. Pityriasis rosea-like drug eruption due to nortriptyline in a patient with vulvodynia. *Journal of lower genital tract disease,* 17**,** 226.

BARAN, R. & BRUN, P. 1986. Photoonycholysis induced by the fluoroquinolones pefloxacine and ofloxacine. *Dermatology,* 173**,** 185-188.

BARBOSA, N. S. & WETTER, D. A. 2014. Bullous phototoxicity from voriconazole. *Journal of Emergency Medicine,* 46**,** e83-e84.

BARKER, J. N., GRIFFITHS, C., NICKOLOFF, B. J., MITRA, R. & DIXIT, V. M. 1991. Keratinocytes as initiators of inflammation. *The Lancet,* 337**,** 211-214.

BARRATT, M. D. 2004. Structure–activity relationships and prediction of the phototoxicity and phototoxic potential of new drugs. *Alternatives to Laboratory Animals,* 32**,** 511-524.

BARTLETT, C., DOYAL, L., EBRAHIM, S., DAVEY, P., BACHMANN, M., EGGER, M. & DIEPPE, P. 2005. The causes and effects of socio-demographic exclusions from clinical trials. *Health Technology Assessment (Winchester, England),* 9**,** iii-152.

BARTON, J. C. & EDWARDS, C. Q. 2016. Porphyria cutanea tarda associated with HFE C282Y homozygosity, iron overload, and use of a contraceptive vaginal ring. *Journal of community hospital internal medicine perspectives,* 6**,** 30380.

BASARAB, T., YU, R. & RUSSELL JONES, R. 1997. Calcium antagonist-induced photo-exposed telangiectasia. *British Journal of Dermatology,* 136**,** 974-975.

BAUER, M., MONZ, B. U., MONTEJO, A. L., QUAIL, D., DANTCHEV, N., DEMYTTENAERE, K., GARCIA-CEBRIAN, A., GRASSI, L., PERAHIA, D. G. & REED, C. 2008. Prescribing patterns of antidepressants in Europe: results from the Factors Influencing Depression Endpoints Research (FINDER) study. *European Psychiatry,* 23**,** 66-73.

BAUMANN, L. 2008. Understanding and treating various skin types: the Baumann Skin Type Indicator. *Dermatologic clinics,* 26**,** 359-373.

BAXTER, B. T., PEARCE, W. H., WALTKE, E. A., LITTOOY, F. N., HALLETT JR, J. W., KENT, K. C., UPCHURCH JR, G. R., CHAIKOF, E. L., MILLS, J. L. & FLECKTEN, B. 2002. Prolonged administration of doxycycline in patients with small asymptomatic abdominal aortic aneurysms: report of a prospective (Phase II) multicenter study. *Journal of vascular surgery,* 36**,** 1-12.

BEATTIE, P. 2006. Solar Urticaria. *Photodermatology. Manson Publishing, London***,** 45-50.

BEITNER, H. 1988. Immediate pigment-darkening reaction. *Photo-dermatology,* 5**,** 96-100.

BELL, H. & RHODES, L. 2000. Photopatch testing in photosensitive patients. *British Journal of Dermatology,* 142**,** 589-590.

BEM JL, M. R., RAWLINS MD. 1988. *update. Review of yellow cards—1986 and 1987* [Online]. [Accessed].

BERGNER, T. & PRZYBILLA, B. 1992. Photosensitization caused by ibuprofen. *Journal of the American Academy of Dermatology,* 26**,** 114-116.

BERNHARD, S., LANG, K. K., AMMANN, R. A., LÜER, S., LEIBUNDGUT, K., DIEPOLD, M. & AEBI, C. 2012. Voriconazole-induced phototoxicity in children. *The Pediatric infectious disease journal,* 31**,** 769-771.

BHALLA, M., GARG, G. & THAMI, G. 2011. Photodistribution of rash in phenytoin-induced drug rash with eosinophilia and systemic symptoms. *Clinical and experimental dermatology (Print),* 36**,** 553-554.

BIRNER, A. M. & MEYER, L. P. 2001. Photosensitivity associated with fluorouracil, prochlorperazine, and topical tretinoin. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy,* 21**,** 258-260.

BISHNOI, A. & VINAY, K. 2019. Butterfly rash, dental staining & painful nails in a child. *The Indian Journal of Medical Research,* 150**,** 103.

BISSET, A. F. 2002. Discontinuation of thioridazine: risks must be balanced. *BMJ: British Medical Journal,* 325**,** 967.

BJELLERUP, M. & LJUNGGREN, B. 1994. Differences in phototoxic potency should be considered when tetracyclines are prescribed during summer-time. A study on doxycycline and lymecycline in human volunteers, using an objective method for recording erythema. *British Journal of Dermatology,* 130**,** 356-360.

BLAKELY, K. M., DRUCKER, A. M. & ROSEN, C. F. 2019. Drug-induced photosensitivity—an update: culprit drugs, prevention and management. *Drug safety***,** 1-21.

BORGIA, F., VACCARO, M., GUARNERI, F. & CANNAVÒ, S. 2000. Photodistributed telangiectasia following use of cefotaxime. *British Journal of Dermatology,* 143**,** 674-675.

BOUYSSOU-GAUTHIER, M.-L., BEDANE, C., BOULINGUEZ, S. & BONNETBLANC, J.-M. 1999. Photosensitivity with sulfasalazopyridine hypersensitivity syndrome. *Dermatology,* 198**,** 388-390.

BOYD, A. E., MODI, S., HOWARD, S. J., MOORE, C. B., KEEVIL, B. G. & DENNING, D. W. 2004. Adverse reactions to voriconazole. *Clinical infectious diseases,* 39**,** 1241-1244.

BOYER, M., KATTA, R. & MARKUS, R. 2003a. Diltiazem-induced photodistributed hyperpigmentation. *Dermatology online journal,* 9**,** 10-10.

BOYER, M., KATTA, R. & MARKUS, R. 2003b. Diltiazem-induced photodistributed hyperpigmentation. *Dermatology online journal,* 9.

BOYLE, J. 1986. Amiodarone-induced cutaneous photosensitivity. *British Journal of Dermatology,* 115**,** 253-254.

BRACKE, A., NIJSTEN, T., VANDERMAESEN, J., MEULEMAN, L. & LAMBERT, J. 2005a. Lansoprazole-induced subacute cutaneous lupus erythematosus: two cases. *ACTA DERMATOVENEREOLOGICA-STOCKHOLM-,* 85**,** 353.

BRACKE, A., NIJSTEN, T., VANDERMAESEN, J., MEULEMAN, L. & LAMBERT, J. 2005b. Lansoprazole-induced subacute cutaneous lupus erythematosus: two cases. *Acta dermato-venereologica,* 1**,** 1-1.

BROESHART, J., KAMMEYER, A. & BOS, J. 2003. European standard regarding clothing and protection against ultraviolet radiation. *Nederlands tijdschrift voor geneeskunde,* 147**,** 2215-2218.

BROWN, C. W. & DENG, J.-S. 1995. Thiazide diuretics induce cutaneous lupus-like adverse reaction. *Journal of Toxicology: Clinical Toxicology,* 33**,** 729-733.

BRUNEL, A. S., FRAISSE, T., LECHICHE, C., PINZANI, V., MAUBOUSSIN, J. M. & SOTTO, A. 2008. Multifocal squamous cell carcinomas in an HIV-infected patient with a long-term voriconazole therapy. *aids,* 22**,** 905-906.

BRUYNZEEL, D., FERGUSON, J., ANDERSEN, K., GONÇALO, M., ENGLISH, J., GOOSSENS, A., HOLZLE, E., IBBOTSON, S., LECHA, M. & LEHMANN, P. 2004. Photopatch testing: a consensus methodology for Europe. *Journal of the European Academy of Dermatology and Venereology,* 18**,** 679-682.

BURCKHARDT, W. & SUTTER, T. 1963. Photoallergic drug exanthema caused by hydrochlorothiazide. *Zeitschrift fur Haut-und Geschlechtskrankheiten,* 34**,** 105-108.

BURDGE, D. R., NAKIELNA, E. & RABIN, H. R. 1995. Photosensitivity associated with ciprofloxacin use in adult patients with cystic fibrosis. *Antimicrobial agents and chemotherapy,* 39**,** 793.

BURRY, J. & LAWRENCE, J. 1976. Phototoxic blisters from high frusemide dosage. *The British journal of dermatology,* 94**,** 495-499.

BYLAITE, M., GRIGAITIENE, J. & LAPINSKAITE, G. 2009. Photodermatoses: classification, evaluation and management. *British Journal of Dermatology,* 161**,** 61-68.

BYUN, J. W., BANG, C. I., YANG, B. H., HAN, S. H., SONG, H. J., LEE, H. S., SHIN, J. H. & CHOI, G. S. 2011. Photodistributed telangiectasia induced by amlodipine. *Annals of dermatology,* 23**,** S30-S32.

CACHEUX, V., MARTASEK, P., FOUGEROUSSE, F., DELFAU, M. H., DRUART, L., TACHDJIAN, G. & GRANDCHAMP, B. 1994. Localization of the human coproporphyrinogen oxidase gene to chromosome band 3q12. *Human genetics,* 94**,** 557-559.

CADET, J., GRAND, A. & DOUKI, T. 2014. Solar UV radiation-induced DNA bipyrimidine photoproducts: formation and mechanistic insights. *Photoinduced phenomena in nucleic acids II.* Springer.

CALLALY, E., FITZGERALD, O. & ROGERS, S. 2008. Hydroxychloroquine-associated, photo-induced toxic epidermal necrolysis. *Clinical and Experimental Dermatology: Clinical dermatology,* 33**,** 572-574.

CALLEN, J. P. Photosensitivity in collagen vascular diseases. Seminars in cutaneous medicine and surgery, 1999. WB Saunders, 293-296.

CALLEN, J. P., HUGHES, A. P. & KULP-SHORTEN, C. 2001. Subacute cutaneous lupus erythematosus induced or exacerbated by terbinafine: a report of 5 cases. *Archives of dermatology,* 137**,** 1196-1198.

CALNAN, C. 1978. Photodermatitis and quinine sensitivity. *Contact dermatitis,* 4**,** 58-58.

CARIOU, C., DROITCOURT, C., OSMONT, M. N., MARGUERY, M. C., DUTARTRE, H., DELAUNAY, J., AVENEL-AUDRAN, M., DUPUY, A. & ADAMSKI, H. 2020. Photodermatitis from topical phenothiazines: A case series. *Contact Dermatitis*.

CHAABANE, H., MASMOUDI, A., AMOURI, M., GHORBEL, S., BOUDAYA, S., HAMMAMI, S., ZGHAL, K. & TURKI, H. 2013. Cutaneous adverse drug reaction: prospective study of 118 cases. *La Tunisie medicale,* 91**,** 514-520.

CHALMERS, R., MUSTON, H. L., SRINIVAS, V. & BENNETT, D. 1982. High incidence of amiodarone-induced photosensitivity in North-west England. *British medical journal (Clinical research ed.),* 285**,** 341.

CHANG, C.-H., CHANG, J. W., HUI, C.-Y. & YANG, C.-H. 2009. Severe photosensitivity reaction to vandetanib. *Journal of Clinical Oncology,* 27**,** e114-e115.

CHENG, M. P., PAQUETTE, K., LANDS, L. C., OVETCHKINE, P., THÉORET, Y. & QUACH, C. 2010. Voriconazole inhibition of vitamin A metabolism: are adverse events increased in cystic fibrosis patients? *Pediatric pulmonology,* 45**,** 661-666.

CHOI, D., KANNAN, S. & LIM, H. W. 2014. Evaluation of patients with photodermatoses. *Dermatologic clinics,* 32**,** 267-75, vii.

CHU, D. H. 2008. Development and structure of skin. *Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill***,** 57-73.

COHEN, J. L. & LIM, H. W. 2000. The cutaneous porphyrias. *Current Problems in Dermatology,* 12**,** 35-40.

COHEN, P. R. 2009. Photodistributed erythema multiforme: paclitaxel-related, photosensitive conditions in patients with cancer. *Journal of drugs in dermatology: JDD,* 8**,** 61-64.

COLEMAN, A., FEDELE, F., KHAZOVA, M., FREEMAN, P. & SARKANY, R. 2010. A survey of the optical hazards associated with hospital light sources with reference to the Control of Artificial Optical Radiation at Work Regulations 2010. *Journal of Radiological Protection,* 30**,** 469.

COLLINS, P. & FERGUSON, J. 1993. Photodistributed nifedipine-induced facial telangictasia. *British Journal of Dermatology,* 129**,** 630-633.

CONLON, J. D., DAUENHAUER, M., TONKOVIC-CAPIN, V., TALANO, J., MARGOLIS, D., DROLET, B. A. & FAIRLEY, J. A. 2008. Voriconazole-induced blistering in the setting of graft versus host disease: A report of 2 patients. *Journal of the American Academy of Dermatology,* 58**,** 484-487.

COOPER, S. & GEORGE, S. 2001. Photosensitivity reaction associated with use of the combined oral contraceptive. *British Journal of Dermatology,* 144**,** 641-642.

COOPER, S. & WOJNAROWSKA, F. 2003. Photo-damage in Northern European renal transplant recipients is associated with use of calcium channel blockers. *Clinical and Experimental Dermatology: Clinical dermatology,* 28**,** 588-591.

CORREIA, O., LOMBA VIANA, H., AZEVEDO, R., DELGADO, L. & POLÓNIA, J. 2001. Possible phototoxicity with subsequent progression to discoid lupus following pantoprazole administration. *Clinical and experimental dermatology,* 26**,** 455-456.

CORTEZ, K. J., WALSH, T. J. & BENNETT, J. E. 2003. Successful treatment of coccidioidal meningitis with voriconazole. *Clinical infectious diseases,* 36**,** 1619-1622.

COSTAGLIOLA, C., MENZIONE, M., CHIOSI, F., ROMANO, M. R., DELLA CORTE, M. & RINALDI, M. 2008. Retinal phototoxicity induced by hydrochlorothiazide after exposure to a UV tanning device. *Photochemistry and photobiology,* 84**,** 1294-1297.

COULSON, I. 1993. 'Fade out'photochromonychia. *Clinical and experimental dermatology,* 18**,** 87-88.

COWEN, E. W., NGUYEN, J. C., MILLER, D. D., MCSHANE, D., ARRON, S. T., PROSE, N. S., TURNER, M. L. & FOX, L. P. 2010. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. *Journal of the American Academy of Dermatology,* 62**,** 31-37.

COZZANI, E., PAPPALARDO, F., GALLO, R. & PARODI, A. 2014. Photosensitivity Induced by Mesalazine: Report of a Case. *The American journal of gastroenterology,* 109**,** 923.

CREWS, P. C., KACHMAN, S. & BEYER, A. G. 1999. Influences on UVR transmission of undyed woven fabrics. *Textile Chemist & Colorist,* 31.

CROUCH, R. B., FOLEY, P. A. & BAKER, C. S. 2003. Analysis of patients with suspected photosensitivity referred for investigation to an Australian photodermatology clinic. *Journal of the American Academy of Dermatology,* 48**,** 714-720.

CUMMINS, R., WAGNER-WEINER, L. & PALLER, A. 2000. Pseudoporphyria induced by celecoxib in a patient with juvenile rheumatoid arthritis. *The Journal of rheumatology,* 27**,** 2938-2940.

CURIGLIANO, G., FORMICA, V., DE PAS, T., SPITALERI, G., PIETRI, E., FAZIO, N., DE BRAUD, F. & GOLDHIRSCH, A. 2006. Life-threatening toxic epidermal necrolysis during voriconazole therapy for invasive aspergillosis after chemotherapy. *Annals of oncology,* 17**,** 1174-1175.

CUTCHIS, P. 1980. A formula comparing annual damaging ultraviolet (DUV) radiation doses at tropical and mid-latitudes. *Final Report High Altitude Pollution Program. US Dept. of Transportation. IDA log# HQ***,** 80-22403.

D'ORAZIO, J., JARRETT, S., AMARO-ORTIZ, A. & SCOTT, T. 2013. UV radiation and the skin. *International journal of molecular sciences,* 14**,** 12222-12248.

DAM, C. 2008. Denmark 801103236 Lansoprazole/omeprazole/pantoprazole Cutaneous lupus erythematosus: 5 case reports. *Reactions,* 1193**,** 15.

DAM, C. & BYGUM, A. 2008. Subacute cutaneous lupus erythematosus induced or exacerbated by proton pump inhibitors. *Acta dermato-venereologica,* 88**,** 87-89.

DARKEN, M. & MCBURNEY, E. I. 1988. Subacute cutaneous lupus erythematosus—like drug eruption due to combination diuretic hydrochlorothiazide and triamterene. *Journal of the American Academy of Dermatology,* 18**,** 38-42.

DATAR, P., KAFLE, P., SCHMIDT, F. M., BHATTARAI, B. & MUKHTAR, O. 2019. Dronedarone-induced Phototoxicity in a Patient with Atrial Fibrillation. *Cureus,* 11.

DAVIS, A. & ROBSON, J. 2016. The dangers of NSAIDs: look both ways. British Journal of General Practice.

DAVIS, S., CAPJACK, L., KERR, N. & FEDOSEJCVS, R. 1997. Clothing as protection from ultraviolet radiation: which fabric is most effective? *International journal of Dermatology,* 36**,** 374-379.

DAWE, R. S. & IBBOTSON, S. H. 2014. Drug-induced photosensitivity. *Dermatologic clinics,* 32**,** 363-368.

DAWSON, T. 1986. Quinine lichenoid photosensitivity. *Clinical and experimental dermatology,* 11**,** 670-671.

DAWSON, T. 1995. Side effect of quinine for nocturnal cramps. *BMJ: British Medical Journal,* 310**,** 738.

DE GUTIERREZ, E. R. & ABACA, H. 2004. Photodistributed lichenoid drug eruption with rhabdomyolysis occurring during leflunomide therapy. *Dermatology,* 208**,** 232-233.

DE KORTE, J., MOMBERS, F. M., SPRANGERS, M. A. & BOS, J. D. 2002. The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Archives of dermatology,* 138**,** 1221-1227.

DE L'ECLAIRAGE, C. I. 1970. International lighting vocabulary. *Paris, CIE*.

DE VERNEUIL, H., NORDMANN, Y., PHUNG, N., GRANDCHAMP, B., AITKEN, G., GRELIER, M. & NOIRE, J. 1978. Familial and sporadic porphyria cutanea: two different diseases. *International Journal of Biochemistry,* 9**,** 927-931.

DELEO, V. A., SUÁREZ, S. M. & MASO, M. J. 1992. Photoallergic contact dermatitis: results of photopatch testing in New York, 1985 to 1990. *Archives of dermatology,* 128**,** 1513-1518.

DELMAS, A. & PLANTIN, P. 1995a. Photosensibilisation à la quinine utilisée dans le traitement des crampes nocturnes essentielles. *La Presse médicale,* 24.

DELMAS, A. & PLANTIN, P. 1995b. Photosensitization induced by quinine used in the treatment of idiopathic nocturnal cramps. *Presse medicale (Paris, France: 1983),* 24**,** 1707-1707.

DENNING, D. & GRIFFITHS, C. 2001. Muco-cutaneous retinoid-effects and facial erythema related to the novel triazole antifungal agent voriconazole. *Clinical and experimental dermatology,* 26**,** 648-653.

DESAI, N., ALEXIS, A. F. & DELEO, V. A. 2010. Facial hyperpigmentation caused by diltiazem hydrochloride. *Cutis,* 86**,** 82-84.

DIFFEY, B. & CHALLONER, A. 1978. Absolute radiation dosimetry in photochemotherapy. *Physics in Medicine & Biology,* 23**,** 1124.

DIFFEY, B., DAYMOND, T. & FAIRGREAVES, H. 1983. Phototoxic reactions to piroxicam, naproxen and tiaprofenic acid. *Rheumatology,* 22**,** 239-242.

DIFFEY, B. & FARR, P. 1988. The action spectrum in drug induced photosensitivity. *Photochemistry and photobiology,* 47**,** 49-53.

DIFFEY, B., FARR, P. & ADAMS, S. 1988. The action spectrum in quinine photosensitivity. *British Journal of Dermatology,* 118**,** 679-685.

DIFFEY, B., JANSEN, C., URBACH, F. & WULF, H. 1997. The standard erythema dose: a new photobiological concept. *Photodermatology, photoimmunology & photomedicine,* 13**,** 64-66.

DIFFEY, B. & OAKLEY, A. 1987. The onset of ultraviolet erythema. *British Journal of Dermatology,* 116**,** 183-187.

DIFFEY, B. L. 2002. What is light? *Photodermatology, photoimmunology & photomedicine,* 18**,** 68-74.

DIFFEY, B. L. 2018. Time and Place as Modifiers of Personal UV Exposure. *International journal of environmental research and public health,* 15**,** 1112.

DIFFEY, B. L. & KOCHEVAR, I. E. 2007. Basic principles of photobiology. *BASIC AND CLINICAL DERMATOLOGY,* 38**,** 15.

DIFFEY, B. L. & LANGTRY, J. 1989. Phototoxic potential of thiazide diuretics in normal subjects. *Archives of dermatology,* 125**,** 1355-1358.

DOGRA, S. & KANWAR, A. 2003. Clopidogrel bisulphate-induced photosensitive lichenoid eruption: first report. *British Journal of Dermatology,* 148**,** 609-610.

DOLAN, C. K., HALL, M. A., BLAZES, D. L. & NORWOOD, C. W. 2004. Pseudoporphyria as a result of voriconazole use: a case report. *International journal of dermatology,* 43**,** 768-771.

DOUKI, T., REYNAUD-ANGELIN, A., CADET, J. & SAGE, E. 2003. Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation. *Biochemistry,* 42**,** 9221-9226.

DRAELOS, Z. D. 2001. Degradation and migration of facial foundations. *Journal of the American Academy of Dermatology,* 45**,** 542-543.

DRUCKER, A. M. & ROSEN, C. F. 2011. Drug-induced photosensitivity. *Drug Safety,* 34**,** 821-837.

DRUCKER, A. M., WANG, A. R., LI, W.-Q., SEVETSON, E., BLOCK, J. K. & QURESHI, A. A. 2017. The burden of atopic dermatitis: summary of a report for the National Eczema Association. *Journal of Investigative Dermatology,* 137**,** 26-30.

DUARTE, J. D. & COOPER-DEHOFF, R. M. 2010. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. *Expert review of cardiovascular therapy,* 8**,** 793-802.

DUFNER, K. S., BUSS, L. A. & KIZITO, J. 2006. Drug-induced photosensitivity. *Hospital Pharmacy,* 41**,** 196-206.

DUGUID, C., O'SULLIVAN, D. & MURPHY, G. 1993. Determination of threshold UV-A elicitation dose in photopatch testing. *Contact Dermatitis,* 29**,** 192-194.

EILERS, S., BACH, D. Q., GABER, R., BLATT, H., GUEVARA, Y., NITSCHE, K., KUNDU, R. V. & ROBINSON, J. K. 2013. Accuracy of self-report in assessing Fitzpatrick skin phototypes I through VI. *JAMA dermatology,* 149**,** 1289-1294.

EL-TAWIL, S., AL MUSA, T., VALLI, H., LUNN, M. P., BRASSINGTON, R., EL-TAWIL, T. & WEBER, M. 2015. Quinine for muscle cramps. *Cochrane database of systematic reviews*.

ELDER, D. E. 2014. *Lever's histopathology of the skin*, Lippincott Williams & Wilkins.

ELDER, G. H., LEE, G. B. & TOVEY, J. A. 1978. Decreased activity of hepatic uroporphyrinogen decarboxylase in sporadic porphyria cutanea tarda. *New England Journal of Medicine,* 299**,** 274-278.

EPAULARD, O., LECCIA, M.-T., BLANCHE, S., CHOSIDOW, O., MAMZER-BRUNEEL, M.-F., RAVAUD, P., THIEBAUT, A., VILLIER, C. & LORTHOLARY, O. 2011. Phototoxicity and photocarcinogenesis associated with voriconazole. *Médecine et maladies infectieuses,* 41**,** 639-645.

EPSTEIN, J. 1971. Adverse cutaneous reactions to the sun. *Year book of dermatology.* Year Book Medical Publishers Chicago.

EPSTEIN, J. H. 1972. Photoallergy: A review. *Archives of dermatology,* 106**,** 741-748.

EPSTEIN, J. H. 1983. Phototoxicity and photoallergy in man. *Journal of the American Academy of Dermatology,* 8**,** 141-147.

EPSTEIN, S. 1962. Photoallergy versus phototoxicity. *Rees, RB: Dermatoses Due to Environmental and Physical Factors, Springfield, Ill: Charles C Thomas, Publisher***,** 119-135.

EPSTEIN, S. & ROWE, R. J. 1957. Photoallergy and photocross-sensitivity to phenergan. *The Journal of investigative dermatology,* 29**,** 319-326.

EPSTEIN, S. J. J. O. I. D. 1939. Photoallergy and primary photosensitivity to sulfanilamide. 2**,** 43-51.

ERBAGCI, Z. 2004. Amlodipine associated hyperpigmentation. *Saudi medical journal,* 25**,** 103-105.

FABBRI, P., CARDINALI, C., GIOMI, B. & CAPRONI, M. 2003. Cutaneous lupus erythematosus. *American journal of clinical dermatology,* 4**,** 449-465.

FALKSON, G. & SCHULZ, E. 1962. SKIN CHANGES IN PATIENTS TREATED WITH 5-FLUOROURACIL. *British Journal of Dermatology,* 74**,** 229-236.

FANOUS, N. 2002. A new patient classification for laser resurfacing and peels: predicting responses, risks, and results. *Aesthetic plastic surgery,* 26**,** 99-104.

FARR, P., DIFFEY, B. & PIERACH, C. 1985. Pseudoporphyria due to naproxen. *The Lancet,* 325**,** 1166-1167.

FARR, P. M., BESAG, J. E. & DIFFEY, B. L. 1988. The time course of UVB and UVC erythema. *Journal of investigative dermatology,* 91**,** 454-457.

FARRAR, M. D., WEBB, A. R., KIFT, R., DURKIN, M. T., ALLAN, D., HERBERT, A., BERRY, J. L. & RHODES, L. E. 2013. Efficacy of a dose range of simulated sunlight exposures in raising vitamin D status in South Asian adults: implications for targeted guidance on sun exposure. *The American journal of clinical nutrition,* 97**,** 1210-1216.

FDA. 2020. *Food and Drug Administration, Novel Drug Approvals 2019* [Online]. Available: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019 [Accessed 3rd July 2019].

FENTON, L., DAWE, R., IBBOTSON, S., FERGUSON, J., SILBURN, S. & MOSELEY, H. 2014. Impact assessment of energy-efficient lighting in patients with lupus erythematosus: a pilot study. *British Journal of Dermatology,* 170**,** 694-698.

FENTON, L., FERGUSON, J. & MOSELEY, H. 2012. Analysis of energy saving lamps for use by photosensitive individuals. *Photochemical & Photobiological Sciences,* 11**,** 1346-1355.

FERGUSON, J. 1986. Amiodarone: a study of cutaneous photosensitivity. *British journal of clinical practice. Supplement,* 44**,** 63-66.

FERGUSON, J. 1995. Fluoroquinolone photosensitization: a review of clinical and laboratory studies. *Photochemistry and photobiology,* 62**,** 954-958.

FERGUSON, J. 2002. Photosensitivity due to drugs. *Photodermatology, photoimmunology & photomedicine,* 18**,** 262-269.

FERGUSON, J. 2003. Phototoxicity due to fluoroquinolones. *Quinolone Antimicrobial Agents, Third Edition.* American Society of Microbiology.

FERGUSON, J. 2006. Chronic actinic dermatitis. *Photodermatology. Manson, London*, 39-43.

FERGUSON, J., ADDO, H., JOHNSON, B. & FRAIN-BELL, W. 1987. Quinine induced photosensitivity: clinical and experimental studies. *British Journal of Dermatology,* 117, 631-640.

FERGUSON, J., ADDO, H., JONES, S., JOHNSON, B. & FRAIN-BELL, W. 1985. A study of cutaneous photosensitivity induced by amiodarone. *British Journal of Dermatology,* 113, 537-549.

FERGUSON, J. & JOHNSON, B. 1989. Retinoid associated phototoxicity and photosensitivity. *Pharmacology & therapeutics,* 40, 123-135.

FERNÁNDEZ-JORGE, B., GODAY-BUJÁN, J., MURGA, M., PIÑEYRO MOLINA, F. & PÉREZ-VARELA, L. 2009. Photoallergic contact dermatitis due to diclofenac with cross-reaction to aceclofenac: two case reports. *Contact dermatitis,* 61, 236-237.

FERNÁNDEZ DE CORES, L., BERNAOLA, G., FERNANDEZ, E., LEANIZBARRUTIA, I. & MUJÑOZ, D. 1987. Photodermatitis from triamterene. *Contact dermatitis,* 17, 114-115.

FERNÁNDEZ, R., JORDÁ, P., FERNÁNDEZ-NAVARRO, J., SALES, A., RAMIRO, A. & MIRALLES, A. Photoxicity reaction due to methotrexate. Anales de pediatria (Barcelona, Spain: 2003), 2012. 179-180.

FINLAY, A. Y. & KHAN, G. 1994. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clinical and experimental dermatology,* 19, 210-216.

FITZPATRICK, T. B. 1988. The validity and practicality of sun-reactive skin types I through VI. *Archives of dermatology,* 124, 869-871.

FITZPATRICK, T. B., SZABO, G. & WICK, M. M. 1983. Biochemistry and physiology of melanin pigmentation. *Biochemistry and physiology of the skin. New York: Oxford University Press*, 687-712.

FLINK, M., BRANDBERG, C. & EKSTEDT, M. 2019. Why patients decline participation in an intervention to reduce re-hospitalization through patient activation: whom are we missing? *Trials,* 20, 82.

FOOD & ADMINISTRATION, D. 1978. Sunscreen drug products for over-the-counter human use. *Federal register,* 43, 38206-38269.

FOOTE, C. S. 2012. Photosensitized Oxidation and Singlet Oxygen: Consequences in. *Free radicals in biology,* 2, 85.

FORMULARY, J. F. C. B. N. 2020. *Joint Formulary Committee British National Formulary*.

FOTIADES, J., SOTER, N. A. & LIM, H. W. 1995. Results of evaluation of 203 patients for photosensitivity in a 7.3-year period. *Journal of the American Academy of Dermatology,* 33, 597-602.

FRAIN-BELL, W. 1985. *Cutaneous photobiology*, Oxford University Press, USA.

FREDERICK, J., SNELL, H. & HAYWOOD, E. 1989. Solar ultraviolet radiation at the earth's surface. *Photochemistry and Photobiology,* 50, 443-450.

FRICK, M. A., SOLER-PALACÍN, P., NALDA, A. M., GUARNER, M. E. & NADAL, C. F. 2010. Photosensitivity in immunocompromised patients receiving long-term therapy with oral voriconazole. *The Pediatric infectious disease journal,* 29, 480-481.

FRIEDMAN, G. D., ASGARI, M. M., WARTON, E. M., CHAN, J. & HABEL, L. A. 2012. Antihypertensive drugs and lip cancer in non-Hispanic whites. *Archives of internal medicine,* 172, 1246-1251.

GABOUREL, J. D. 1963. Effects of hydroxychloroquine on the growth of mammalian cells in vitro. *Journal of Pharmacology and Experimental Therapeutics,* 141, 122-130.

GALEA, S. & TRACY, M. 2007. Participation rates in epidemiologic studies. *Annals of epidemiology,* 17**,** 643-653.

GAMBICHLER, T., ALTMEYER, P. & HOFFMANN, K. 2002. Role of clothes in sun protection. *Cancers of the Skin.* Springer.

GAMBICHLER, T., LAPERRE, J. & HOFFMANN, K. 2006. The European standard for sun-protective clothing: EN 13758. *Journal of the European Academy of Dermatology and Venereology,* 20**,** 125-130.

GAMBICHLER, T., ROTTERDAM, S., ALTMEYER, P. & HOFFMANN, K. 2001. Protection against ultraviolet radiation by commercial summer clothing: need for standardised testing and labelling. *BMC dermatology,* 1**,** 6.

GARDEAZABAL, J., GONZALEZ, M., IZU, R., GIL, N., AGUIRRE, A. & DIAZ-PEREZ, J. 1993. Phenofibrate-induced lichenoid photodermatitis. *Photodermatology, photoimmunology & photomedicine,* 9**,** 156-158.

GAUFBERG, E. & ELLISON, J. M. 1995a. Photosensitivity reaction to fluoxetine. *The Journal of clinical psychiatry,* 56**,** 486-486.

GAUFBERG, E. & ELLISON, J. M. 1995b. Photosensitivity reaction to fluoxetine. *The Journal of clinical psychiatry,* 56.

GHAZI, S., COUTEAU, C. & COIFFARD, L. 2010. What level of protection can be obtained using sun protective clothing? Determining effectiveness using an in vitro method. *International journal of pharmaceutics,* 397**,** 144-146.

GLIEM, N., BROEKAERT, S., SEITZ, C., SCHÖN, M. & ELLENRIEDER, V. 2017a. Esomeprazol-induced cutaneous lupus erythematosus. *Zeitschrift fur Gastroenterologie,* 55**,** 861.

GLIEM, N., BROEKAERT, S. M. C., SEITZ, C. S., SCHÖN, M. P. & ELLENRIEDER, V. 2017b. Esomeprazol-induzierter kutaner Lupus erythematodes. *Zeitschrift für Gastroenterologie,* 55**,** 861-865.

GLOGAU, R. 1994. Chemical peeling and aging skin. *J Geriatr Dermatol,* 2**,** 30-35.

GODAY BUJAN, J., GARCÍA ALVAREZ-EIRE, G., MARTINEZ, W., DEL POZO, J. & FONSECA, E. 2001. Photoallergic contact dermatitis from aceclofenac. *Contact dermatitis,* 45.

GOLDMAN, M. P. 2008. Universal classification of skin type. *Simplified Facial Rejuvenation.* Springer.

GÓMEZ-BERNAL, S., ÁLVAREZ-PÉREZ, A., RODRÍGUEZ-PAZOS, L., GUTIÉRREZ-GONZÁLEZ, E., RODRÍGUEZ-GRANADOS, M. T. & TORIBIO, J. 2014. Photosensitivity due to thiazides. *Actas Dermo-Sifiliográficas (English Edition),* 105**,** 359-366.

GÓMEZ-BERNAL, S., LOUREIRO, M., RODRÍGUEZ-GRANADOS, M. T. & TORIBIO, J. 2010. Systemic photosensitivity due to a contraceptive patch. *Photodermatology, photoimmunology & photomedicine,* 26**,** 213-215.

GONZALEZ-ARRIAGADA, W. A., SILVA, A., VARGAS, P. A., DE ALMEIDA, O. P. & LOPES, M. A. 2013. Facial pigmentation associated with amiodarone. *Gen. Dent,* 61**,** e15-e17.

GOULD, J. W., MERCURIO, M. G. & ELMETS, C. A. 1995. Cutaneous photosensitivity diseases induced by exogenous agents. *Journal of the American Academy of Dermatology,* 33**,** 551-573.

GOUYA, L., DEYBACH, J. C., LAMORIL, J., DA SILVA, V., BEAUMONT, C., GRANDCHAMP, B. & NORDMANN, Y. 1996. Modulation of the phenotype in dominant erythropoietic protoporphyria by a low expression of the normal ferrochelatase allele. *American journal of human genetics,* 58**,** 292.

GRABCZYNSKA, S. & COWLEY, N. 2000. Amlodipine induced-photosensitivity presenting as telangiectasia. *British Journal of Dermatology,* 142**,** 1255-1256.

GRABCZYNSKA, S., MCGREGOR, J., KONDEATIS, E., VAUGHAN, R. & HAWK, J. 1999. Actinic prurigo and polymorphic light eruption: common pathogenesis and the importance of HLA-DR4/DRB1* 0407. *British Journal of Dermatology,* 140**,** 232-236.

GRANADOS, M., TORRE, C., CRUCES, M. J. & PINEIRO, G. 1998. Chronic actinic dermatitis due to simvastatin. *Contact dermatitis,* 38**,** 294-295.

GREGORIOU, S., KARAGIORGA, T., STRATIGOS, A., VOLONAKIS, K., KONTOCHRISTOPOULOS, G. & RIGOPOULOS, D. 2008. Photo-onycholysis caused by olanzapine and aripiprazole. *Journal of clinical psychopharmacology,* 28**,** 219-220.

GRÖNHAGEN, C., FORED, C., LINDER, M., GRANATH, F. & NYBERG, F. 2012. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case–control study of 234 patients in Sweden. *British Journal of Dermatology,* 167**,** 296-305.

GROSE, E. & RAMIEN, M. 2019. Interstitial granulomatous drug reaction related to hydrochlorothiazide. *Dermatology online journal,* 25.

GROUP, B. P. 1997. Workshop report Photopatch testing-methods and indications. *British Journal of Dermatology,* 136**,** 371-376.

GUPTA, V. & SHARMA, V. K. 2019. Skin typing: Fitzpatrick grading and others. *Clinics in dermatology,* 37**,** 430-436.

GUTIÉRREZ-GONZÁLEZ, E., RODRÍGUEZ-PAZOS, L., RODRÍGUEZ-GRANADOS, M. T. & TORIBIO, J. 2011. Photosensitivity induced by naproxen. *Photodermatology, photoimmunology & photomedicine,* 27**,** 338-340.

GUZZO, C. & KAIDBEY, K. 1990. Persistent light reactivity from systemic quinine. *Photodermatology, photoimmunology & photomedicine,* 7**,** 166-168.

HABIF, T. P. 2006. Doxycycline-induced phototoxicity. *New England Journal of Medicine,* 355**,** 182-182.

HAFIJI, J. & BATCHELOR, J. 2010. Red in the face. *Bmj,* 340**,** b5643.

HALEVY, S., GRUNWALD, M., FEUERMAN, E. & LIVNI, E. 1986. Lichenoid eruption due to hydrochlorothiazide. Diagnostic aid of macrophage migration inhibition factor (MIF) test. *Annals of allergy,* 56**,** 402-405.

HAMADA, K., SAWADA, Y., YAMAGUCHI, T., OHMORI, S., OMOTO, D., HARUYAMA, S., YOSHIOKA, M., NISHIO, D. & NAKAMURA, M. 2016. Photosensitivity due to tocilizumab presenting with erythema multiforme-like lesions. *European Journal of Dermatology,* 26**,** 503-504.

HANSON, M. & PETRONIC-ROSIC, V. 2008. Reticulated phototoxic eruption in a patient on long-term diltiazem therapy. *Journal of drugs in dermatology: JDD,* 7**,** 792-793.

HARBER, L., BICKERS, D., EPSTEIN, J., PATHAK, M. & URBACH, F. 1974. Report on ultraviolet light sources. Report by the task force on photobiology of the national program for dermatology. *Archives of dermatology,* 109**,** 833.

HARBER, L., BICKERS, D. & LAMOLA, A. 1989. Principles of light absorption and photochemistry. *Photosensitivity Diseases. WB Saunders Co.; Second ed., Philadelphia*.

HARBER, L., LC, H. & DR, B. 1975. The porphyrias: Basic science aspects, clinical diagnosis and management.

HARBER, L. C. & BICKERS, D. R. 1989. *Photosensitivity diseases: principles of diagnosis and treatment*, Mosby.

HARBER, L. C., LASHINSKY, A. M. & BAER, R. L. 1959a. Photosensitivity due to chlorothiazide and hydrochlorothiazide. *New England Journal of Medicine,* 261**,** 1378-1381.

HARBER, L. C., LASHINSKY, A. M. & BAER, R. L. 1959b. Skin manifestations of photosensitivity due to chlorothiazide and hydrochlorothiazide. *The Journal of investigative dermatology,* 33**,** 83-84.

HARRIS, L., MCKENNA, W., ROWLAND, E., HOLT, D., STOREY, G. & KRIKLER, D. 1983. Side effects of long-term amiodarone therapy. *Circulation,* 67**,** 45-51.

HARRISON, G. I. & YOUNG, A. R. 2002. Ultraviolet radiation-induced erythema in human skin. *Methods,* 28**,** 14-19.

HARRISON, S., ALDERDICE, F., HENDERSON, J., REDSHAW, M. & QUIGLEY, M. A. 2020. Trends in response rates and respondent characteristics in five National Maternity Surveys in England during 1995–2018. *Archives of Public Health,* 78**,** 1-11.

HASAN, T., PERTOVAARA, M., YLI-KERTTULA, U., LUUKKAALA, T. & KORPELA, M. 2004. Seasonal variation of disease activity of systemic lupus erythematosus in Finland: a 1 year follow up study. *Annals of the rheumatic diseases,* 63**,** 1498-1500.

HATCH, K. L. & OSTERWALDER, U. 2006. Garments as solar ultraviolet radiation screening materials. *Dermatologic clinics,* 24**,** 85-100.

HATHAWAY, J. A. & SLINEY, D. H. 2002. VISIBLE LIGHT and INFRARED RADIATION. *Physical and Biological Hazards of the Workplace***,** 203-208.

HAWK, J., MURPHY, G. & HOLDEN, C. 1988. The presence of neutrophils in human cutaneous ultraviolet-B inflammation. *British Journal of Dermatology,* 118**,** 27-30.

HAWK, J., YOUNG, A. & FERGUSON, J. 2010. Cutaneous photobiology. *Rook's Textbook of Dermatology,* 1**,** 1-24.

HAWKES, N. 2017. NICE guidelines could put 12 million UK adults on statins. British Medical Journal Publishing Group.

HAWKINS, C. L., MORGAN, P. E. & DAVIES, M. J. 2009. Quantification of protein modification by oxidants. *Free Radical Biology and Medicine,* 46**,** 965-988.

HAYLETT, A., FELTON, S., DENNING, D. & RHODES, L. 2013. Voriconazole-induced photosensitivity: photobiological assessment of a case series of 12 patients. *British Journal of Dermatology,* 168**,** 179-185.

HAYLETT, A. K., KOUMAKI, D. & RHODES, L. E. 2018. Solar urticaria in 145 patients: Assessment of action spectra and impact on quality of life in adults and children. *Photodermatology, photoimmunology & photomedicine,* 34**,** 262-268.

HAYLETT, A. K. & RHODES, L. E. 2009. Evaluation of the Patient with Photosensitivity. *Allergy Frontiers: Diagnosis and Health Economics.* Springer.

HAYS, G. B., LYLE, C. B. & WHEELER, C. E. 1964. Slate-gray color in patients receiving chlorpromazine. *Archives of dermatology,* 90**,** 471-476.

HEALTH, N. I. O. 2017. Livertox: clinical and research information on drug-induced liver injury. *Nih. gov https://livertox. nih. gov*.

HEBERT, A. A. & RALSTON, J. P. 2001. Cutaneous reactions to anticonvulsant medications. *The Journal of clinical psychiatry,* 62**,** 22-26.

HEERFORDT, I. M., PHILIPSEN, P. A. & CHRISTIAN WULF, H. 2017. Long-term trend in sunscreen use among beachgoers in Denmark. *Acta Dermato-Venereologica,* 97**,** 1202-1205.

HEERFORDT, I. M., TORSNES, L. R., PHILIPSEN, P. A. & WULF, H. C. 2018. Sunscreen use optimized by two consecutive applications. *PloS one,* 13**,** e0193916.

HEYDENREICH, G., PINDBORG, T. & SCHMIDT, H. 1977. Bullous dermatosis among patients with chronic renal failure on high dose frusemide. *Acta Medica Scandinavica,* 202**,** 61-64.

HICKEY, J. R., DUNNILL, G. S. & SANSOM, J. E. 2007. Photoallergic reaction to systemic quinine sulphate. *Contact dermatitis,* 57**,** 384-386.

HICKMAN, G., DUVAL, A., PICARD, C. & PETIT, A. Porphyria cutanea tarda revealed by voriconazole. Annales de dermatologie et de venereologie, 2010. 36-39.

HILL, V., CHOW, J., COWLEY, N. & MARSDEN, R. 2003. Subacute lupus erythematosus-like eruption due to terbinafine: report of three cases. *British journal of dermatology (1951),* 148.

HINTON, W., MCGOVERN, A., COYLE, R., HAN, T. S., SHARMA, P., CORREA, A., FERREIRA, F. & DE LUSIGNAN, S. 2018. Incidence and prevalence of cardiovascular disease in English primary care: a cross-sectional and follow-up study of the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC). *BMJ open,* 8**,** e020282.

HOFBAUER, G., ATTARD, N., HARWOOD, C., MCGREGOR, J., DZIUNYCZ, P., IOTZOVA-WEISS, G., STRAUB, G., MEYER, R., KAMENISCH, Y. & BERNEBURG, M. 2012. Reversal of UVA skin photosensitivity and DNA damage in kidney transplant recipients by replacing azathioprine. *American Journal of Transplantation,* 12**,** 218-225.

HOFFMANN, K., CASETTI, F. & SCHEMPP, C. 2015. Methotrexate-associated photosensitization. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete,* 66**,** 459-461.

HOFMANN, G. A., GRADL, G., SCHULZ, M., HAIDINGER, G., TANEW, A. & WEBER, B. 2020. The frequency of photosensitizing drug dispensings in Austria and Germany: a correlation with their photosensitizing potential based on published literature. *Journal of the European Academy of Dermatology and Venereology,* 34**,** 589-600.

HOLME, S., PEARSE, A. & ANSTEY, A. 2002. Chronic actinic dermatitis secondary to simvastatin. *Photodermatology, photoimmunology & photomedicine,* 18**,** 313-314.

HÖLZLE, E., NEUMANN, N., HAUSEN, B., PRZYBILLA, B., SCHAUDER, S., HÖNIGSMANN, H., BIRCHER, A. & PLEWIG, G. 1991. Photopatch testing: the 5-year experience of the German, Austrian, and Swiss Photopatch Test Group. *Journal of the American Academy of Dermatology,* 25**,** 59-68.

HONGBO, Y., THOMAS, C. L., HARRISON, M. A., SALEK, M. S. & FINLAY, A. Y. 2005. Translating the science of quality of life into practice: what do dermatology life quality index scores mean? *Journal of Investigative Dermatology,* 125**,** 659-664.

HÖNIGSMANN, H. 2002. Erythema and pigmentation. *Photodermatology, photoimmunology & photomedicine,* 18**,** 75-81.

HORIUCHI, Y. & SHIMAKURA, S. 1999a. Mesalazine and photosensitivity. *The American journal of gastroenterology,* 94**,** 3386-3387.

HORIUCHI, Y. & SHIMAKURA, S. 1999b. Mesalazine and photosensitivity. *American Journal of Gastroenterology,* 94**,** 3386-3387.

HORKAY, I., TAMASI, P., PREKOPA, A. & DALMY, L. 1975. Photodermatoses induced by oral contraceptives. *Archives of Dermatological Research,* 253**,** 53-61.

HUANG, D. B., WU, J. J. & LAHART, C. J. 2004. Toxic epidermal necrolysis as a complication of treatment with voriconazole. *Southern medical journal,* 97**,** 1116-1118.

HUANG, H.-T., CHANG, C.-L. & TZENG, D.-S. 2010. Toxic epidermal necrolysis after sun-exposure probably due to lamotrigine and chlorpromazine. *Asian journal of psychiatry,* 3**,** 240-242.

HUNG, R., SANGLE, S., BENTON, E., D'CRUZ, D. & MCGIBBON, D. 2015. Proton pump inhibitor-induced subcutaneous lupus erythematosus in a patient with systemic lupus erythematosus. *Clinical and experimental dermatology,* 40**,** 808-809.

HUNTER, J., BHUTANI, L. & MAGNUS, I. 1970. Chlorpromazine photosensitivity in mice: its action spectrum and the effect of anti-inflammatory agents. *British Journal of Dermatology,* 82**,** 157-168.

HUSSAIN, S., ANDERSON, D. N., SALVATTI, M. E., ADAMSON, B., MCMANUS, M. & BRAVERMAN, A. S. 2000. Onycholysis as a complication of systemic chemotherapy. *Cancer,* 88**,** 2367-2371.

I˚ NALÖZ, H. S., KIRTAK, N., HERKEN, H., ÖZGÖZTAŞI, O. & AYNACIOĞLU, A. Ş. 2001. Citalopram-induced photopigmentation. *The Journal of dermatology,* 28**,** 742-745.

IBBOTSON, S. H. & FARR, P. M. 1999. The time-course of psoralen ultraviolet A (PUVA) erythema. *Journal of investigative dermatology,* 113**,** 346-349.

IBSEN, H. & LASTHEIN, A. B. 1982. Photo-onycholysis due to tetracycline-hydrochloride. *Acta dermato-venereologica,* 63**,** 555-557.

IOULIOS, P., CHARALAMPOS, M. & EFROSSINI, T. 2003. The spectrum of cutaneous reactions associated with calcium antagonists: a review of the literature and the possible etiopathogenic mechanisms. *Dermatology online journal,* 9**,** 6-6.

ITAKURA, A., TANI, Y., KANEKO, N. & HIDE, M. 2018. Impact of chronic urticaria on quality of life and work in Japan: Results of a real-world study. *The Journal of dermatology,* 45**,** 963-970.

ITRI, R., JUNQUEIRA, H. C., MERTINS, O. & BAPTISTA, M. S. 2014. Membrane changes under oxidative stress: the impact of oxidized lipids. *Biophysical reviews,* 6**,** 47-61.

JAKA, A., LÓPEZ-PESTAÑA, A., TUNEU, A., LOBO, C., LÓPEZ-NÚÑEZ, M. & ORMAECHEA, N. 2011. Photodistributed reticulated hyperpigmentation related to diltiazem. *Dermatology online journal,* 17**,** 14-14.

JAMES, W. D., ELSTON, D. & BERGER, T. 2011. *Andrew's Diseases of the Skin E-Book: Clinical Dermatology*, Elsevier Health Sciences.

JEANMOUGIN, M., SIGAL, S. & CIVATTE, J. Photoallergy to quinine. Annales de dermatologie et de vénéréologie, 1984. 565-567.

JENSEN, A., THOMSEN, H., ENGEBJERG, M., OLESEN, A., SØRENSEN, H. & KARAGAS, M. 2008. Use of photosensitising diuretics and risk of skin cancer: a population-based case–control study. *British Journal of Cancer,* 99**,** 1522-1528.

JIYAD, Z., OLSEN, C., BURKE, M., ISBEL, N. & GREEN, A. C. 2016. Azathioprine and risk of skin cancer in organ transplant recipients: systematic review and meta-analysis. *American Journal of Transplantation,* 16**,** 3490-3503.

JOHNSON, B., ZAYNOUN, S., GARDINER, J. & FRAIN-BELL, W. 1975. A study of persistent light reaction in quindoxin and quinine photosensitivity. *British Journal of Dermatology,* 93**,** 21-22.

JOHNSON, B. E., GIBBS, N. K. & FERGUSON, J. 1997. Quinolone antibiotic with potential to photosensitize skin tumorigenesis. *Journal of Photochemistry and Photobiology B: Biology,* 37**,** 171-173.

JOHNSTON, G. & COULSON, I. 2002. Thiazide-induced lichenoid photosensitivity. *Clinical and experimental dermatology,* 27**,** 670-672.

JOHNSTON, G., COULSON, I. J. C. & DERMATOLOGY, E. 2002. Thiazide-induced lichenoid photosensitivity. 27**,** 670-672.

JONG, C. T., FINLAY, A. Y., PEARSE, A. D., KERR, A., FERGUSON, J., BENTON, E., HAWK, J., SARKANY, R., MCMULLEN, E. & RHODES, L. 2008. The quality of life of 790 patients with photodermatoses. *British Journal of Dermatology,* 159**,** 192-197.

JOSEPH, M. S. 1987. Photodermatitis provoked by dapsone: a case report. *Lepr Rev,* 58**,** 425-8.

JOVANOVIC, Z., SCHORNSTEIN, T., SUTOR, A., NEUFANG, G. & HAGENS, R. 2017. Conventional sunscreen application does not lead to sufficient body coverage. *International journal of cosmetic science,* 39**,** 550-555.

K SINGH, L., SAHU, M. & K PRAHARAJ, S. 2015. Olanzapine-induced reversible pellagroid skin lesion. *Current drug safety,* 10**,** 251-253.

KANNAN, V., WILKINSON, K. E., VARGHESE, M., LYNCH-MEDICK, S., WILLETT, D. L., BOSLER, T. A., CHU, L., GATES, S. I., HOLBEIN, M. B. & WILLETT, M. M. 2019. Count me in: using a patient portal to minimize implicit bias in clinical research recruitment. *Journal of the American Medical Informatics Association,* 26**,** 703-713.

KANWAR, A., DHAR, S. & GHOSH, S. 1993a. Photosensitive lichenoid eruption due to enalapril. *Dermatology,* 187**,** 80-80.

KANWAR, A., DHAR, S. & GHOSH, S. 1993b. Photosensitive lichenoid eruption due to enalapril. *DERMATOLOGY-BASEL-,* 187**,** 80-80.

KANWAR, A., GUPTA, R., DAS, M. S. & KAUR, S. 1990. Photosensitivity due to alprazolam. *Dermatologica,* 181**,** 75.

KAR, B. R. 2008. Dapsone-induced photosensitivity: a rare clinical presentation. *Photodermatology, photoimmunology & photomedicine,* 24**,** 270-271.

KASTALLI, S., EL, S. A., CHAABANE, A., AMRANI, R., DAGHFOUS, R. & BELKAHIA, C. 2009. Photosensitivity induced by metformin: a report of 3 cases. *La Tunisie medicale,* 87**,** 703-705.

KATIYAR, S. K., BIHARI, S. & PRAKASH, S. 2010. Pyrazinamide-induced phototoxicity: a case report and review of literature. *Indian journal of dermatology,* 55**,** 113.

KAWADA, A. 1986. UVB-induced erythema, delayed tanning, and UVA-induced immediate tanning in Japanese skin. *Photo-dermatology,* 3**,** 327-333.

KERR, A. C., FERGUNSON, J., HAYLETT, A., RHODES, L., GONÇALO, M. & TASKFORCE, E. M. P. T. S. 2012. A European multicentre photopatch test study.

KERR, H. A. & LIM, H. W. 2007. Photodermatoses in African Americans: a retrospective analysis of 135 patients over a 7-year period. *Journal of the American Academy of Dermatology,* 57**,** 638-643.

KHAN, A. J., MARGHOOB, A. A., PRESTIA, A. E. & SPECTOR, I. J. 2000. Methotrexate and the photodermatitis reactivation reaction: a case report and review of the literature. *Cutis,* 66**,** 379-382.

KHANDPUR, S., PORTER, R., BOULTON, S. & ANSTEY, A. 2016. Drug-induced photosensitivity: new insights into pathomechanisms and clinical variation through basic and applied science. *British Journal of Dermatology*.

KHANDPUR, S., PORTER, R., BOULTON, S. & ANSTEY, A. 2017. Drug-induced photosensitivity: new insights into pathomechanisms and clinical variation through basic and applied science. *British Journal of Dermatology,* 176**,** 902-909.

KHOO, S., TAY, Y. & THAM, S. 1996. Photodermatoses in a Singapore skin referral centre. *Clinical and experimental dermatology,* 21**,** 263-268.

KIM, K., PARK, H. & LIM, K.-M. 2015. Phototoxicity: Its mechanism and animal alternative test methods. *Toxicological research,* 31**,** 97-104.

KIM, T., KANG, J., LEE, H. & YOUN, J. 1995. Two cases of mequitazine-induced photosensitivity reactions. *Photodermatology, photoimmunology & photomedicine,* 11**,** 170-173.

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**,** 1069-1075.

KIRSHBAUM, B. & BEERMAN, H. 1964. PHOTOSENSITIZATION DUE TO DRUGS: A REVIEW OF SOME OF THE RECENT LITERATURE. *The American journal of the medical sciences,* 248**,** 445-468.

KOCATÜRK, E., KÖKLÜ, N., GÜNGÖR, Ş., ÜLKÜMEN, P. K., BAHÇETEPE, N. & ERHAN, S. Ş. 2014. Solar burn reactivation reaction: an unusual side effect of methotrexate. *Photodermatology, photoimmunology & photomedicine,* 30**,** 338-339.

KOLLIAS, N. 1995. The spectroscopy of human melanin pigmentation, Melanin: Its Role in Human Photoprotection. Valdenmar Publishing Co.

KONDO, S., KAGAYA, M., YAMADA, Y., MATSUSAKA, H. & JIMBOW, K. 2000. UVB photosensitivity due to ranitidine. *Dermatology,* 201**,** 71-73.

KORZENIOWSKA, K., CIEŚLEWICZ, A., CHMARA, E., JABŁECKA, A. & PAWLACZYK, M. 2019. Photosensitivity reactions in the elderly population: questionnaire-based survey and literature review. *Therapeutics and clinical risk management,* 15**,** 1111.

KOWALZICK, L. & ZIEGLER, H. 2006. Photoallergic contact dermatitis from topical diclofenac in Solaraze® gel. *Contact Dermatitis,* 54**,** 348-349.

KRUTMANN, J. 2000. Ultraviolet A radiation-induced biological effects in human skin: relevance for photoaging and photodermatosis. *Journal of dermatological science,* 23**,** S22-S26.

KUBO, Y., FUKUMOTO, D., ISHIGAMI, T., HIDA, Y. & ARASE, S. 2010. Diltiazem-associated photodistributed hyperpigmentation: report of two Japanese cases and published work review. *The Journal of dermatology,* 37**,** 807-811.

KULLAVANIJAYA, P. & LIM, H. W. 2005. Photoprotection. *Journal of the American Academy of Dermatology,* 52**,** 937-958.

KUO, S., MENON, K. & KUNDU, R. V. 2014. Photosensitivity reaction from dronedarone for atrial fibrillation. *Cutis,* 94**,** E10-1.

KUO, S. & SIVAMANI, R. K. 2014. UVB-sensitive solar urticaria possibly associated with terbinafine. *Dermatology online journal,* 20.

KUPPER, T. S., CHUA, A. O., FLOOD, P., MCGUIRE, J. & GUBLER, U. 1987. Interleukin 1 gene expression in cultured human keratinocytes is augmented by ultraviolet irradiation. *The Journal of clinical investigation,* 80**,** 430-436.

KURUMAJI, Y. & SHONO, M. 1994. Drug-induced solar urticaria due to repirinast. *Dermatology,* 188**,** 117-121.

KUS, S., YUCELTEN, D. & AYTUG, A. 2005. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of acne vulgaris. *Clinical and Experimental Dermatology: Clinical dermatology,* 30**,** 215-220.

KUSHNER, J. P. 1982. The enzymatic defect in porphyria cutanea tarda. Mass Medical Soc.

KUWATSUKA, S., KUWATSUKA, Y., TAKENAKA, M. & UTANI, A. 2016. Case of photosensitivity caused by fenofibrate after photosensitization to ketoprofen. *The Journal of dermatology,* 43**,** 224-225.

KUZNETSOV, A. V., WEISENSEEL, P., FLAIG, M. J., RUZICKA, T. & PRINZ, J. C. 2011. Photoallergic erythroderma due to doxycycline therapy of erythema chronicum migrans. *Acta dermato-venereologica,* 91**,** 734-736.

LADEMANN, J., SCHANZER, S., JACOBI, U., SCHAEFER, H., PFLU, F., DRILLER, H., BECK, J., MEINKE, M., ROGGAN, A. & STERRY, W. 2005. Synergy effects between organic and inorganic UV filters in sunscreens. *Journal of biomedical optics,* 10**,** 014008-0140087.

LADIZINSKI, B. & ELPERN, D. J. 2013. Dronaderone-induced phototoxicity. *Journal of drugs in dermatology: JDD,* 12**,** 946-947.

LANCER, H. A. 1998. Lancer ethnicity scale (LES). *Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery,* 22**,** 9-9.

LAUTENSCHLAGER, S., WULF, H. C. & PITTELKOW, M. R. 2007. Photoprotection. *The Lancet,* 370**,** 528-537.

LAYTON, A. & CUNLIFFE, W. 1993. Phototoxic eruptions due to doxycycline—a dose-related phenomenon. *Clinical and experimental dermatology,* 18**,** 425-427.

LE CORRE, Y., LÉONARD, F., FERTIN, C. & KALIS, B. Granuloma-annulare type photosensitivity disorder caused by diclofenac. Annales de dermatologie et de venereologie, 1992. 932.

LEE, A. Y. & JUNG, S. 1998. Two patients with isoniazid-induced photosensitive lichenoid eruptions confirmed by photopatch test. *Photodermatology, photoimmunology & photomedicine,* 14**,** 77-78.

LEENUTAPHONG, V. & MANUSKIATTI, W. 1996. Fenofibrate-induced photosensitivity. *Journal of the American Academy of Dermatology,* 35**,** 775-776.

LEÓN-MATEOS, A., ZULAICA, A., CAEIRO, J., FABEIRO, J., CALVIÑO, S., PETEIRO, C. & TORIBIO, J. 2007. Photo-induced granulomatous eruption by hydroxyurea. *Journal of the European Academy of Dermatology and Venereology,* 21**,** 1428-1429.

LEONG, Y. 1970. Promethazine photosensitive dermatitis. *Singapore Med J,* 11**,** 52-54.

LEROY, D., DOMPMARTIN, A., LORIER, E., LEPORT, Y. & AUDEBERT, C. 1990. Photosensitivity induced by fenofibrate. *Photodermatology,* 7**,** 136-138.

LEROY, D., DOMPMARTIN, A., SZCZURKO, C., MICHEL, M. & LOUVET, S. 1997. Photodermatitis from ketoprofen with cross-reactivity to fenofibrate and benzophenones. *Photodermatology, photoimmunology & photomedicine,* 13**,** 93-97.

LEVY, M. L., BARRON, K. S., EICHENFIELD, A. & HONIG, P. J. 1990. Naproxen-induced pseudoporphyria: a distinctive photodermatitis. *The Journal of pediatrics,* 117**,** 660-664.

LEWIS, V. & FINLAY, A. Y. 10 years experience of the Dermatology Life Quality Index (DLQI). Journal of Investigative Dermatology Symposium Proceedings, 2004. Elsevier, 169-180.

LIM, C. & PETERS, T. 1984. Urine and faecal porphyrin profiles by reversed-phase high-performance liquid chromatography in the porphyrias. *Clinica chimica acta,* 139**,** 55-63.

LIM, D. & MURPHY, G. 2003. High-level ultraviolet A photoprotection is needed to prevent doxycycline phototoxicity: lessons learned in East Timor. *British Journal of Dermatology,* 149**,** 213-214.

LIM, D. S. & TRISCOTT, J. 2003. O'Brien's actinic granuloma in association with prolonged doxycycline phototoxicity. *Australasian journal of dermatology,* 44**,** 67-70.

LIM, H. W., HOENIGSMANN, H. & HAWK, J. L. M. 2007a. *Photodermatology,* New York, N.Y. ; London, Informa Healthcare.

LIM, H. W., HONIGSMANN, H. & HAWK, J. L. 2007b. *Photodermatology*, CRC Press.

LIN, N.-C., CHOU, J.-Y., CHEN, H. & CHEN, V. C.-H. 2009. Sertraline-induced photoallergic reaction. *Journal of clinical psychopharmacology,* 29**,** 95-96.

LINDQUIST, M. 2008. *VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Information*

Journal [Online]. World Health Organisation Collaborating Centre for International Drug Monitoring (2020). . Available: http://www.vigiaccess.org/

[Accessed 10th July 2020

].

LING, T. C., GIBBS, N. K. & RHODES, L. E. 2003. Treatment of polymorphic light eruption. *Photodermatology, photoimmunology & photomedicine,* 19**,** 217-227.

LIPSKY, B. A. & BAKER, C. A. 1999. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clinical Infectious Diseases,* 28**,** 352-361.

LISI, P., ASSALVE, D. & HANSEL, K. 2004. Phototoxic and photoallergic dermatitis caused by hydroxychloroquine. *Contact dermatitis,* 50**,** 255-256.

LIU, W., LAI, W., WANG, X., LI, L., TIAN, Y., LU, Y., WU, Y., LI, Y., ZHANG, P. & WU, Y. 2006. Skin phototyping in a Chinese female population: analysis of four hundred and four cases from four major cities of China. *Photodermatology, photoimmunology & photomedicine,* 22**,** 184-188.

LIUNGGREN, B., HINDSÉN, M. & ISAKSSON, M. 1992. Systemic quinine photosensitivity with photoepicutaneous cross-reactivity to quinidine. *Contact dermatitis,* 26**,** 1-4.

LJUNGGREN, B. & BJELLERUP, M. J. P.-D. 1986. Systemic drug photosensitivity. 3**,** 26-35.

LJUNGGREN, B. & SJÖVALL, P. 1986. Systemic quinine photosensitivity. *Archives of dermatology,* 122**,** 909-911.

LOFT, N. D., EGEBERG, A., RASMUSSEN, M. K., BRYLD, L. E., GNIADECKI, R., DAM, T. N., IVERSEN, L. & SKOV, L. 2019. Patient-reported Outcomes During Treatment in Patients with Moderate-to-severe Psoriasis: A Danish Nationwide Study. *Acta Dermato-Venereologica,* 99**,** 1224-1230.

LOWE, G., HENDERSON, C., GRAU, R., HANSEN, C. & SONTHEIMER, R. 2011. A systematic review of drug-induced subacute cutaneous lupus erythematosus. *British Journal of Dermatology,* 164**,** 465-472.

LUGER, S. W., PAPARONE, P., WORMSER, G. P., NADELMAN, R. B., GRUNWALDT, E., GOMEZ, G., WISNIEWSKI, M. & COLLINS, J. J. 1995. Comparison of cefuroxime axetil and doxycycline in treatment of patients with early Lyme disease associated with erythema migrans. *Antimicrobial agents and chemotherapy,* 39**,** 661-667.

LUTON, E. & FINCHUM, R. 1965. Photosensitivity reaction to chlordiazepoxide. *Archives of dermatology,* 91**,** 362-363.

LÜTZOW-HOLM, C. 1991. Naproxen-induced bullous photodermatitis (pseudoporphyria). *Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke,* 111**,** 2739-2740.

LYDE, C. B. & BERGSTRESSER, P. R. 1997. Ultraviolet protection from sun avoidance. *Dermatologic Therapy,* 4**,** 72-78.

MACHET, L., VAILLANT, L., JAN, V. & LORETTE, G. 1997. Fenofibrate-induced photosensitivity: value of photopatch testing. *Journal of the American Academy of Dermatology,* 37**,** 808-809.

MAERKER, J., HARM, A., FOELDVARI, I. & HÖGER, P. 2001. Naproxeninduzierte pseudoporphyrie. *Der Hautarzt,* 52**,** 1026-1029.

MAGNUS, I. 1976. Artificial sources for irradiation. *Dermatological photobiology. Blackwell, Oxford*, 41-53.

MAHMOUD, B. H., HEXSEL, C. L., HAMZAVI, I. H. & LIM, H. W. 2008. Effects of visible light on the skin. *Photochemistry and photobiology,* 84, 450-462.

MALANI, A. N. & ARONOFF, D. M. 2008. Voriconazole-induced photosensitivity. *Clinical medicine & research,* 6, 83-85.

MALLORY, S. & BERRY, D. 1986. Severe reactivation of sunburn following methotrexate use. *Pediatrics,* 78, 514.

MANKIA, S., RYTINA, E. & BURROWS, N. 2010. Omeprazole-induced subacute cutaneous lupus erythematosus. *Clinical and experimental dermatology,* 35.

MANTEUFFEL, M., WILLIAMS, S., CHEN, W., VERBRUGGE, R. R., PITTMAN, D. G. & STEINKELLNER, A. 2014. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *Journal of women's health,* 23, 112-119.

MARESCA, V., FLORI, E., BRIGANTI, S., CAMERA, E., CARIO-ANDRÉ, M., TAÏEB, A. & PICARDO, M. 2006. UVA-induced modification of catalase charge properties in the epidermis is correlated with the skin phototype. *Journal of Investigative Dermatology,* 126, 182-190.

MARGUERY, M.-C., CHOUINI-LALANNE, N., DRUGEON, C., GADROY, A., BAYLE, P., JOURNE, F., BAZEX, J. & D'INCAN, M. 2006. UV-B phototoxic effects induced by atorvastatin. *Archives of dermatology,* 142, 1065-1086.

MARIONNET, C., TRICAUD, C. & BERNERD, F. 2015. Exposure to non-extreme solar UV daylight: spectral characterization, effects on skin and photoprotection. *International journal of molecular sciences,* 16, 68-90.

MARKHAM, A. 2017. Brigatinib: first global approval. *Drugs,* 77, 1131-1135.

MARSDEN, J., WHITE, M., ANNAND, F., BURKINSHAW, P., CARVILLE, S., EASTWOOD, B., KELLEHER, M., KNIGHT, J., O'CONNOR, R. & TRAN, A. 2019. Medicines associated with dependence or withdrawal: a mixed-methods public health review and national database study in England. *The Lancet Psychiatry,* 6, 935-950.

MARTÍN-LÁZARO, J., BUJÁN, J. G., ARRONDO, A. P., LOZANO, J. R., GALINDO, E. C. & CAPDEVILA, E. F. 2004. Is photopatch testing useful in the investigation of photosensitivity due to flutamide? *Contact dermatitis,* 50, 325-326.

MASUOKA, E., BITO, T., SHIMIZU, H. & NISHIGORI, C. 2011. Dysfunction of melanocytes in photoleukomelanoderma following photosensitivity caused by hydrochlorothiazide. *Photodermatology, photoimmunology & photomedicine,* 27, 328-330.

MATOS, T. R. & SHETH, V. 2016. The symbiosis of phototherapy and photoimmunology. *Clinics in dermatology,* 34, 538-547.

MATSUO, I., OZAWA, A., NÜZUMA, K. & OHKIDO, M. 1979. Lichenoid dermatitis due to chlorpromazine phototoxicity. *Dermatology,* 159, 46-49.

MATTHIEU, L., MEULEMAN, L., VAN HECKE, E., BLONDEEL, A., DEZFOULIAN, B., CONSTANDT, L. & GOOSSENS, A. 2004. Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis,* 50, 238-241.

MCCARTHY, K. L., PLAYFORD, E. G., LOOKE, D. F. & WHITBY, M. 2007. Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. *Clinical Infectious Diseases,* 44, e55-e56.

MCGRATH, J., EADY, R. & POPE, F. 2010. Anatomy and organization of human skin. *Rook's textbook of dermatology,* 1, 3.1-3.15.

MCGREGOR, J. M., GRABCZYNSKA, S., HAWK, J. L., VAUGHAN, R. & LEWIS, C. M. 2000. Genetic modeling of abnormal photosensitivity in families with polymorphic light eruption and actinic prurigo. *Journal of investigative dermatology,* 115**,** 471-476.

MCKINLAY, A. 1987. A reference action spectrum for ultraviolet erythema in human skin. *CIE journal,* 6**,** 17-22.

MEALEY, K. L., DASSANAYAKE, S. & BURKE, N. S. 2014. Tyrosine kinase inhibitors enhance ciprofloxacin-induced phototoxicity by inhibiting ABCG2. *Oncology,* 87**,** 364-370.

MECCA, P., TOBIN, E. & ANDREW CARLSON, J. 2004. Photo-distributed neutrophilic drug eruption and adult respiratory distress syndrome associated with antidepressant therapy. *Journal of cutaneous pathology,* 31**,** 189-194.

MEDEIROS, V. & LIM, H. 2010. Sunscreens in the management of photodermatoses. *Skin Therapy Lett,* 15**,** 1-3.

MEHLHORN, A. J. & BROWN, D. A. 2007. Infectious Diseases: Safety Concerns with Fluoroquinolones. *Annals of Pharmacotherapy,* 41**,** 1859-1866.

MENDHEKAR, D. & INAMDAR, A. 2009. Mirtazapine and hyperpigmentation. *The World Journal of Biological Psychiatry,* 10**,** 688-689.

METAYER, I., BALGUERIE, X., COURVILLE, P., LAURET, P. & JOLY, P. Photodermatosis induced by hydroxychloroquine: 4 cases. Annales de dermatologie et de venereologie, 2001. 729-731.

MILLARD, T. P. & HAWK, J. L. 2002. Photosensitivity disorders. *American journal of clinical dermatology,* 3**,** 239-246.

MILLER, D. D., COWEN, E. W., NGUYEN, J. C., MCCALMONT, T. H. & FOX, L. P. 2010. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. *Archives of dermatology,* 146**,** 300-304.

MILLER, F. & RAMPLING, D. 1982. Adverse effects of combined propranolol and chlorpromazine therapy. *The American journal of psychiatry,* 139**,** 1198-1199.

MITCHNICK, M. A., FAIRHURST, D. & PINNELL, S. R. 1999. Microfine zinc oxide (Z-cote) as a photostable UVA/UVB sunblock agent. *Journal of the American Academy of Dermatology,* 40**,** 85-90.

MIYAUCHI, H., HORIKI, S. & HORIO, T. 1994. Clinical and experimental photosensitivity reaction to tilisolol hydrochloride. *Photodermatology, photoimmunology & photomedicine,* 10**,** 255-258.

MOHAMED, K. 1988. Severe photodermatitis during ketoconazole therapy. *Clinical and experimental dermatology,* 13**,** 54-54.

MOHAMMED, F., WALLY, L. L., KARABAN, J. E., REDDY, V. B. & LERTRATANAKUL, Y. 2017. Fenofibrate-Induced Lichenoid Drug Eruption: A Rare Culprit. *Case reports in dermatology,* 9**,** 236-242.

MÖLLER, H. 1969. Reactivation of acute inflammation by methotrexate. *Journal of Investigative Dermatology,* 52**,** 437-441.

MONK, B. 1990. Amiodarone-induced photosensitivity and basal-cell carcinoma. *Clinical and experimental dermatology,* 15**,** 319-320.

MONTANARO, S., LHIAUBET-VALLET, V., IESCE, M., PREVITERA, L. & MIRANDA, M. A. 2008. A mechanistic study on the phototoxicity of atorvastatin: singlet oxygen generation by a phenanthrene-like photoproduct. *Chemical research in toxicology,* 22**,** 173-178.

MONTEIRO, A. F., RATO, M. & MARTINS, C. 2016a. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. *Clinics in dermatology,* 34**,** 571-581.

MONTEIRO, A. F., RATO, M. & MARTINS, C. J. C. I. D. 2016b. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. 34**,** 571-581.

MONTORO, J., RODRIGUEZ, M., DIAZ, M. & BERTOMEU, F. 2003. Photoallergic contact dermatitis due to diclofenac. *Contact dermatitis,* 48**,** 115-115.

MOORE, D. E. 2002. Drug-induced cutaneous photosensitivity. *Drug safety,* 25**,** 345-372.

MOORE, D. E. & HEMMENS, V. J. 1982. Photosensitization by antimalarial drugs. *Photochemistry and photobiology,* 36**,** 71-77.

MOORE, M. & MCCOLL, K. 1987. 3L, Rimington C, Goldberg A. Disorders of porphyrin metabolism. New York: Plenum Medical.

MORGADO, F., CALVÃO, J., BARATA, F. & GONÇALO, M. 2019. Phototoxic reaction to brigatinib–a new photosensitizing drug. *Journal of the European Academy of Dermatology and Venereology,* 33**,** e491-e492.

MORIDE, Y., HARAMBURU, F., REQUEJO, A. A. & BEGAUD, B. 1997. Under-reporting of adverse drug reactions in general practice. *British journal of clinical pharmacology,* 43**,** 177-181.

MORIMOTO, K., KAWADA, A., HIRUMA, M., ISHIBASHI, A. & BANBA, H. 1995. Photosensitivity to simvastatin with an unusual response to photopatch and photo tests. *Contact dermatitis,* 33.

MORISON, W. L. 2003. Photoprotection by clothing. *Dermatologic therapy,* 16**,** 16-22.

MOSELEY, H., CAMERON, H., MACLEOD, T., CLARK, C., DAWE, R. & FERGUSON, J. 2001. New sunscreens confer improved protection for photosensitive patients in the blue light region. *British Journal of Dermatology,* 145**,** 789-794.

MOSELEY, H., NAASAN, H., DAWE, R. S., WOODS, J. & FERGUSON, J. 2009. Population reference intervals for minimal erythemal doses in monochromator phototesting. *Photodermatology, photoimmunology & photomedicine,* 25**,** 8-11.

MOSTAFA, N., PHAN, K. & SMITH, S. D. 2020. Mycophenolate mofetil and lichen planopilaris: systematic review and meta-analysis. *Journal of Dermatological Treatment***,** 1-16.

MOTA, A., VASCONCELOS, C., CORREIA, T., BARROS, M. & MESQUITA-GUIMARÃES, J. 1998. Rilmenidine-induced photosensitivity reaction. *Photodermatology, photoimmunology & photomedicine,* 14**,** 132-133.

MOTLEY, R. J. 1990. Pseudoporphyria due to dyazide in a patient with vitiligo. *BMJ: British Medical Journal,* 300**,** 1468.

MURAYAMA, N., IMAI, N., NAKANE, T., SHIMIZU, M. & YAMAZAKI, H. 2007. Roles of CYP3A4 and CYP2C19 in methyl hydroxylated and N-oxidized metabolite formation from voriconazole, a new anti-fungal agent, in human liver microsomes. *Biochemical pharmacology,* 73**,** 2020-2026.

NACHER, M., MCGREADY, R., LERMOO, C., WICHIPONPIBOON, J. & NOSTEN, F. 2005. Photoallergy to quinine. *Tropical doctor,* 35**,** 117-117.

NAGPAL, N., GORDON-ELLIOTT, J. & LIPNER, S. 2019. Comparison of quality of life and illness perception among patients with acne, eczema, and psoriasis. *Dermatology Online Journal,* 25.

NAKAMURA, M., HENDERSON, M., JACOBSEN, G. & LIM, H. W. 2014. Comparison of photodermatoses in A frican-A mericans and C aucasians: a follow-up study. *Photodermatology, photoimmunology & photomedicine,* 30**,** 231-236.

NAKAO, S., HATAHIRA, H., SASAOKA, S., HASEGAWA, S., MOTOOKA, Y., UEDA, N., ABE, J., FUKUDA, A., NAGANUMA, M. & KANOH, H. 2017. Evaluation of drug-induced photosensitivity using

the Japanese Adverse Drug Event Report (JADER) database. *Biological and Pharmaceutical Bulletin,* 40**,** 2158-2165.

NAKATANI, K., KUROSE, T., HYO, T., WATANABE, K., YABE, D., KAWAMOTO, T. & SEINO, Y. 2012. Drug-induced generalized skin eruption in a diabetes mellitus patient receiving a dipeptidyl peptidase-4 inhibitor plus metformin. *Diabetes Therapy,* 3**,** 14.

NARDI, G., LHIAUBET-VALLET, V., LEANDRO-GARCIA, P. & MIRANDA, M. A. 2011. Potential phototoxicity of rosuvastatin mediated by its dihydrophenanthrene-like photoproduct. *Chemical research in toxicology,* 24**,** 1779-1785.

NARURKAR, V., SMOLLER, B. R., HU, C.-H. & BAUER, E. A. 1993. Desipramine-induced blue-gray photosensitive pigmentation. *Archives of dermatology,* 129**,** 474-476.

NATKUNARAJAH, J., STITSON, R. & HARLAND, C. 2010a. A florid rash during summer. *Clinical and experimental dermatology,* 35.

NATKUNARAJAH, J., STITSON, R. & HARLAND, C. 2010b. A florid rash during summer. *Clinical and experimental dermatology,* 35**,** e83-e84.

NEIMAN, R. & FYE, K. 1985. Methotrexate induced false photosensitivity reaction. *The Journal of rheumatology,* 12**,** 354-355.

NEUMANN, N., HÖLZLE, E., LEHMANN, P., BENEDIKTER, S., TAPERNOUX, B. & PLEWIG, G. 1994. Pattern analysis of photopatch test reactions. *Photodermatology, photoimmunology & photomedicine,* 10**,** 65-73.

NEWILL, R. 1960. Photosensitivity caused by promethazine. *British medical journal,* 2**,** 359.

NGUYEN, T. A. & KRAKOWSKI, A. C. 2016. The "Heart Sign": an early indicator of dose-dependent doxycycline-induced phototoxicity. *Pediatric dermatology,* 33**,** e69-e71.

NHS Business Services Authority 2020. English Prescribing Dataset: December 2019.

NHS. Digital 2020. *Patients registered at GP practices*

1st September 2020 [Online]. Available: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/general-practice-data-hub/patients-registered-at-a-gp-practice [Accessed].

NORINS, A. L. 1959. Chlorothiazide drug eruption involving photosensitization. *AMA archives of dermatology,* 79**,** 592-592.

NOWAKOWSKI, J., NADELMAN, R. B., FORSETER, G., MCKENNA, D. & WORMSER, G. P. 1995. Doxycycline versus tetracycline therapy for Lyme disease associated with erythema migrans. *Journal of the American Academy of Dermatology,* 32**,** 223-227.

O'GORMAN, S. M. & MURPHY, G. M. 2014. Photosensitizing medications and photocarcinogenesis. *Photodermatology, photoimmunology & photomedicine,* 30**,** 8-14.

O'REILLY, F., MCKENNA, D. & MURPHY, G. 1999. Is monochromatic irradiation testing useful in the differentiation of drug-induced photosensitivity from chronic actinic dermatitis? *Clinical and experimental dermatology,* 24**,** 118-121.

OGBOLI, M. & RHODES, L. 2000. Chronic actinic dermatitis in young atopic dermatitis sufferers. *British Journal of Dermatology,* 142**,** 845-845.

OGRINC, K., LOGAR, M., LOTRIČ-FURLAN, S., CERAR, D., RUŽIĆ-SABLJIĆ, E. & STRLE, F. 2006. Doxycycline versus ceftriaxone for the treatment of patients with chronic Lyme borreliosis. *Wiener klinische Wochenschrift,* 118**,** 696-701.

OHSHIMA, A., SEO, N., TAKIGAWA, M. & TOKURA, Y. 2000. Formation of antigenic quinolone photoadducts on Langerhans cells initiates photoallergy to systemically administered quinolone in mice. *Journal of investigative dermatology,* 114**,** 569-575.

OKUN, M., HENNER, M. & PAULSON, C. 1994. A quinine-induced drug reaction of photosensitive distribution with histological features mimicking mycosis fungoides. *Clinical and experimental dermatology,* 19**,** 246-248.

OLUMIDE, Y. M. 1987. Photodermatoses in Lagos. *International journal of dermatology,* 26**,** 295-299.

ONOUE, S., SETO, Y., SATO, H., NISHIDA, H., HIROTA, M., ASHIKAGA, T., API, A. M., BASKETTER, D. & TOKURA, Y. 2017. Chemical photoallergy: photobiochemical mechanisms, classification, and risk assessments. *Journal of dermatological science,* 85**,** 4-11.

OTHMAN, F., CARD, T. R. & CROOKS, C. J. 2016. Proton pump inhibitor prescribing patterns in the UK: a primary care database study. *Pharmacoepidemiology and drug safety,* 25**,** 1079-1087.

OUINN, A., DIFFEY, B., CRAIG, P. & FARR, P. 1994. Definition of the minimal erythemal dose used for diagnostic phototesting. *British Journal of Dermatology,* 131**,** 56-56.

OXHOLM, A., OXHOLM, P., STABERG, B. & BENDTZEN, K. 1988. Immunohistological detection of interleukin I-like molecules and tumour necrosis factor in human epidermis before and after UVB-irradiation in vivo. *The British journal of dermatology,* 118**,** 369.

PANTING, K. 2009. Subacute cutaneous lupus erythematosus: case report. *Reactions,* 1270**,** 19.

PANTING, K., PINTO, M. & ELLISON, J. 2009. Lansoprazole-induced subacute cutaneous lupus erythematosus. *Clinical and experimental dermatology,* 34**,** 733-734.

PARISER, D. M. & TAYLOR, J. R. 1975. Quinidine photosensitivity. *Archives of dermatology,* 111**,** 1440-1443.

PARODI, A., ROMAGNOLI, M. & REBORA, A. 1989. Subacute cutaneous lupus erythematosus-like eruption caused by hydrochlorothiazide. *Photo-dermatology,* 6**,** 100.

PARRISH, J. A., JAENICKE, K. F. & ANDERSON, R. R. 1982. Erythema and melanogenesis action spectra of normal human skin. *Photochemistry and Photobiology,* 36**,** 187-191.

PASSIER, A., SMITS-VAN HERWAARDEN, A. & VAN PUIJENBROEK, E. 2004. Photo-onycholysis associated with the use of doxycycline. *Bmj,* 329**,** 265.

PATEL, A. R., PATEL, A. R., SINGH, S., SINGH, S. & KHAWAJA, I. 2019. Treating Allergic Bronchopulmonary Aspergillosis: A Review. *Cureus,* 11.

PATEL, R. M. & MARFATIA, Y. 2008. Clinical study of cutaneous drug eruptions in 200 patients. *Indian Journal of Dermatology, Venereology, and Leprology,* 74**,** 430.

PATHAK, M. & STRATTON, K. 1968. Free radicals in human skin before and after exposure to light. *Archives of biochemistry and biophysics,* 123**,** 468-476.

PAZZAGLI, L., BANFI, R., BORSELLI, G. & SEMMOLA, M. 1998. Photosensitivity reaction to fluoxetine and alprazolam. *Pharmacy World and Science,* 20**,** 136-136.

PAZZAGLIA, M., VENTURI, M. & TOSTI, A. 2014. Photo-onycholysis caused by an unusual beach game activity: a pediatric case of a side effect caused by doxycycline. *Pediatric dermatology,* 31**,** e26-e27.

PEREZ-PEREZ, L., CABANILLAS, M., FERREIRÓS, M. P., PETEIRO, C. & TORIBIO, J. 2007. Photosensitive lichenoid eruption and inhaled tiotropium bromide. *Dermatology,* 214**,** 97-98.

PÉREZ-FEAL, P., PITA DA VEIGA SEIJO, G., MOREIRAS-ARIAS, N., ALISTE-SANTOS, C. & RODRÍGUEZ GRANADOS, M. T. 2020. Systemic photosensitivity due to pregabalin. *Photodermatology, Photoimmunology & Photomedicine*.

PERRETT, C., WALKER, S., O'DONOVAN, P., WARWICK, J., HARWOOD, C., KARRAN, P. & MCGREGOR, J. 2008. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. *British Journal of Dermatology,* 159**,** 198-204.

PETERSEN, B. & WULF, H. C. 2014. Application of sunscreen− theory and reality. *Photodermatology, photoimmunology & photomedicine,* 30**,** 96-101.

PIRMOHAMED, M., JAMES, S., MEAKIN, S., GREEN, C., SCOTT, A. K., WALLEY, T. J., FARRAR, K., PARK, B. K. & BRECKENRIDGE, A. M. 2004. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *Bmj,* 329**,** 15-19.

PRECIADO, S. M., TOMASZEWSKI, D., CHEETHAM, T. C., GREGORIAN, T., XAVIOER, S. & FAWAZ, S. 2020. National gender differences in the prescribing of opioid medications from 2006 to 2015. *Journal of opioid management,* 16**,** 197-208.

QURESHI, Z. P., SEOANE-VAZQUEZ, E., RODRIGUEZ-MONGUIO, R., STEVENSON, K. B. & SZEINBACH, S. L. 2011. Market withdrawal of new molecular entities approved in the United States from 1980 to 2009. *Pharmacoepidemiology and drug safety,* 20**,** 772-777.

RABAR, D., COMBEMALE, P. & PEYRON, F. 2004. Doxycycline-induced photo-onycholysis. *Journal of travel medicine,* 11**,** 386-387.

RACETTE, A. J., ROENIGK, H. H., HANSEN, R., MENDELSON, D. & PARK, A. 2005. Photoaging and phototoxicity from long-term voriconazole treatment in a 15-year-old girl. *Journal of the American Academy of Dermatology,* 52**,** S81-S85.

RAISON-PEYRON, N., MINH, H., PEYRON, J., DEMOLY, P. & GUILLOT, B. 2005. Photodistributed cutaneous drug reaction induced by proton pump inhibitors. *Therapie,* 60**,** 85-87.

RAM-WOLF, C., MAHE, E. & SAIAG, P. 2008. Escitalopram photo-induced erythroderma. *Journal of the European Academy of Dermatology and Venereology,* 22**,** 1015-1017.

RAMACHANDRAN, S. M., LEVENTHAL, J. S., FRANCO, L. G., MIR, A., WALTERS, R. F. & FRANKS, A. G. 2017. Topical drug-induced subacute cutaneous lupus erythematosus isolated to the hands. *Lupus science & medicine,* 4**,** e000207.

RAMÍREZ, A., PEREZ-PEREZ, L., FERNANDEZ-REDONDO, V. & TORIBIO, J. 2007. Photoallergic dermatitis induced by diltiazem. *Contact dermatitis,* 56**,** 118-119.

RAMOS, P., SANTANA, R., CIMA, J., MARQUES, P., BAPTISTA, A., MORENO, L. & MACEDO, A. 2015. Participation rates in Epidemiologic studiesPedro Ramos. *European Journal of Public Health,* 25.

RAPPERSBERGER, K., HÖNIGSMANN, H., ORTEL, B., TANEW, A., KONRAD, K. & WOLFF, K. 1989. Photosensitivity and hyperpigmentation in amiodarone-treated patients: incidence, time course, and recovery. *Journal of investigative dermatology,* 93**,** 201-209.

RASMUSSEN, H., BRANDRUP, F. & THOMSEN, K. 1988. Persistent light reactivity after prochlorperazine treatment. *Ugeskrift for laeger,* 150**,** 930-931.

RAVNBAK, M. H. 2010. Objective determination of Fitzpatrick skin type. *Dan Med Bull,* 57**,** B4153.

REDDY, B. & DAS, S. 2018. Olanzapine-induced photo-allergic reaction. *Australian & New Zealand Journal of Psychiatry,* 52**,** 807-808.

REED, B., HUFF, J., JONES, S., ORTON, P., LEE, L. & NORRIS, D. 1985a. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Annals of internal medicine,* 103**,** 49-51.

REED, B., HUFF, J., JONES, S., ORTON, P., LEE, L. & NORRIS, D. J. A. O. I. M. 1985b. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. 103**,** 49-51.

REED, B. R., HUFF, J. C., JONES, S. K., ORTON, P. W., LEE, L. A. & NORRIS, D. A. 1985c. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Annals of internal medicine,* 103**,** 59-51.

REID, C. D. 1996. Chemical photosensitivity: another reason to be careful in the sun. *FDA Consumer magazine (May 1996). Available: http://permanent. access. gpo. gov/lps1609/www. fda. gov/fdac/features/496_su*.

REĬNGARDENE, D. & ZHILENE, V. 2005. Dermatological adverse reactions of amiodarone. *Kardiologiia,* 45**,** 27-30.

RHODES, L., JOYCE, M., WEST, D., STRICKLAND, I. & FRIEDMANN, P. 1996. Comparison of changes in endothelial adhesion molecule expression following UVB irradiation of skin and a human dermal microvascular cell line (HMEC-1). *Photodermatology, photoimmunology & photomedicine,* 12**,** 114-121.

RHODES, L. E., BOCK, M., JANSSENS, A. S., LING, T. C., ANASTASOPOULOU, L., ANTONIOU, C., AUBIN, F., BRUCKNER, T., FAIVRE, B. & GIBBS, N. K. 2010. Polymorphic light eruption occurs in 18% of Europeans and does not show higher prevalence with increasing latitude: multicenter survey of 6,895 individuals residing from the Mediterranean to Scandinavia. *The Journal of investigative dermatology,* 130**,** 626.

RHODES, L. E. & LIM, H. W. 2007. The acute effects of ultraviolet radiation on the skin. *BASIC AND CLINICAL DERMATOLOGY,* 38**,** 75.

RICCIARDI, L., FEDELE, R., MAZZEO, L., SAITTA, S., MANCUSO, V. & ISOLA, S. 2003. Adverse reactions to pantoprazole. *Scandinavian journal of gastroenterology,* 38**,** 800.

RICHARD, M., FISZENSON, F., JREISSATI, M., JEAN, M. P. & GROB, J. Cutaneous adverse effects during selective serotonin reuptake inhibitors therapy: 2 cases. Annales de dermatologie et de venereologie, 2001. 759-761.

RICHARDSON, P., HAWKEY, C. J. & STACK, W. A. 1998. Proton pump inhibitors. *Drugs,* 56**,** 307-335.

RICHARZ, N., AGUILERA, J., CASTILLO, G., FUENTE, M., FERRÁNDIZ, C. & CARRASCOSA, J. 2017. Phototoxic reaction to a combined oral contraceptive (levonorgestrel/ethinylestradiol). *Photochemical & Photobiological Sciences,* 16**,** 1381-1383.

RIVERS, J. K. & BARNETSON, R. S. 1989. Naproxen-induced bullous photodermatitis. *Medical Journal of Australia,* 151**,** 167-168.

RIZWAN, M., REDDICK, C. L., BUNDY, C., UNSWORTH, R., RICHARDS, H. L. & RHODES, L. E. 2013. Photodermatoses: environmentally induced conditions with high psychological impact. *Photochemical & Photobiological Sciences,* 12**,** 182-189.

ROBERTS, W. E. 2008. The Roberts Skin Type Classification System. *Journal of drugs in dermatology: JDD,* 7**,** 452-456.

ROBINSON, H. N., MORISON, W. L. & HOOD, A. F. 1985. Thiazide diuretic therapy and chronic photosensitivity. *Archives of dermatology,* 121**,** 522-524.

RODRIGUEZ-SERNA, M., VELASCO, M., MIQUEL, J., DE LA CUADRA, J. & ALIAGA, A. 1999. Photoallergic contact dermatitis from Zovirax® cream. *Contact dermatitis,* 41**,** 54-55.

RODRÍGUEZ-PAZOS, L., GÓMEZ-BERNAL, S., MONTERO, I., RODRÍGUEZ-GRANADOS, M. & TORIBIO, J. 2011. Erythema multiforme photoinduced by paroxetine and herpes simplex virus. *Photodermatology, photoimmunology & photomedicine,* 27**,** 219-221.

RODRÍGUEZ-PAZOS, L., SÁNCHEZ-AGUILAR, D., RODRÍGUEZ-GRANADOS, M., PEREIRO-FERREIRÓS, M. & TORIBIO, J. 2010. Erythema multiforme photoinduced by statins. *Photodermatology, photoimmunology & photomedicine,* 26**,** 216-218.

RODRÍGUEZ GRANADOS, M., ABALDE, T., GARCÍA DOVAL, I. & DE LA TORRE, C. 2004. Systemic photosensitivity to quinapril. *Journal of the European Academy of Dermatology and Venereology,* 18**,** 389-390.

RODRIGUEZ GRANADOS, M., DE LA TORRE, C., CRUCES, M. J. & PINEIRO, G. 1998. Chronic actinic dermatitis due to simvastatin. *Contact dermatitis,* 38**,** 294-295.

ROELANDTS, R. 1998. Shedding light on sunscreens. *Clinical and experimental dermatology,* 23**,** 147-157.

ROELANDTS, R. 2007. History of human photobiology.

ROENIGK, H. H., FOWLER-BERGFELD, W. & CURTIS, G. H. 1969. Methotrexate for psoriasis in weekly oral doses. *Archives of Dermatology,* 99**,** 86-93.

ROFFEY, S., COLE, S., COMBY, P., GIBSON, D., JEZEQUEL, S., NEDDERMAN, A., SMITH, D., WALKER, D. & WOOD, N. 2003. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. *Drug Metabolism and Disposition,* 31**,** 731-741.

RÖHRS, S., GEISER, F. & CONRAD, R. 2012. Citalopram-induced subacute cutaneous lupus erythematosus—first case and review concerning photosensitivity in selective serotonin reuptake inhibitors. *General hospital psychiatry,* 34**,** 541-545.

ROJAS MORA, E., MARTÍNEZ SÁNCHEZ, D., HERNÁNDEZ-NÚÑEZ, A. & BORBUJO MARTÍNEZ, J. 2017. Amlodipine-Associated Photodistributed Telangiectasia.

RONGIOLETTI, F. & REBORA, A. 1986. Drug eruption from trazodone. *Journal of the American Academy of Dermatology,* 14**,** 274-275.

ROSENTHAL, A. & HERRMANN, J. 2019. Hydrochlorothiazide-induced photosensitivity in a psoriasis patient following exposure to narrow-band ultraviolet B excimer therapy. *Photodermatology, photoimmunology & photomedicine,* 35**,** 369-371.

ROUPE, G., LARKÖ, O. & OLSSON, S. 1987. Amiodarone photoreactions. *Acta dermato-venereologica,* 67**,** 76-79.

RUBENSTEIN, M., LEVY, M. L. & METRY, D. 2004. Voriconazole-Induced Retinoid-Like Photosensitivity in Children. *Pediatric dermatology,* 21**,** 675-678.

RUTHERFORD, T. & SINCLAIR, R. 2007. Photo-onycholysis due to indapamide. *Australasian journal of dermatology,* 48**,** 35-36.

RUTTER, K., ASHRAF, I., CORDINGLEY, L. & RHODES, L. 2020. Quality of life and psychological impact in the photodermatoses: a systematic review. *British Journal of Dermatology,* 182**,** 1092-1102.

SACHDEVA, S. 2009. Fitzpatrick skin typing: Applications in dermatology. *Indian Journal of Dermatology, Venereology, and Leprology,* 75**,** 93.

SACHS, G., SHIN, J., BESANCON, M. & PRINZ, C. 1993. The continuing development of gastric acid pump inhibitors. *Alimentary pharmacology & therapeutics,* 7**,** 4-12.

SAHA, A., DAS, N. K., HAZRA, A., GHARAMI, R. C., CHOWDHURY, S. N. & DATTA, P. K. 2012. Cutaneous adverse drug reaction profile in a tertiary care out patient setting in eastern India. *Indian journal of pharmacology,* 44**,** 792.

SALADI, R. N., COHEN, S. R., PHELPS, R. G., PERSAUD, A. N. & RUDIKOFF, D. 2006. Diltiazem induces severe photodistributed hyperpigmentation: case series, histoimmunopathology, management, and review of the literature. *Archives of dermatology,* 142**,** 206-210.

SALATHÉ, M. 2016. Digital pharmacovigilance and disease surveillance: combining traditional and big-data systems for better public health. *The Journal of infectious diseases,* 214**,** S399-S403.

SÁNCHEZ-BORGES, M. & GONZÁLEZ-AVELEDO, L. 2011. Photoallergic reactions to angiotensin converting enzyme inhibitors. *Journal of the European Academy of Dermatology and Venereology,* 5**,** 621-622.

SANDHOLDT, L., LAURINAVICIENE, R. & BYGUM, A. 2014. Proton pump inhibitor-induced subacute cutaneous lupus erythematosus. *British Journal of Dermatology,* 170**,** 342-351.

SARAVOLATZ, L. D., JOHNSON, L. B. & KAUFFMAN, C. A. 2003. Voriconazole: a new triazole antifungal agent. *Clinical infectious diseases,* 36**,** 630-637.

SARKANY, I. 1967. The Editor,'The British Journal of Dermatology'. Lichen planus following quinidine therapy. *British Journal of Dermatology,* 79**,** 123-123.

SARKAR, A. K. 2007. On the relationship between fabric processing and ultraviolet radiation transmission. *Photodermatology, photoimmunology & photomedicine,* 23**,** 191-196.

SATANOVE, A. 1965. Pigmentation due to phenothiazines in high and prolonged dosage. *Jama,* 191**,** 263-268.

SATANOVE, A. & MCINTOSH, J. S. 1967. Phototoxic reactions induced by high doses of chlorpromazine and thioridazine. *Jama,* 200**,** 209-212.

SCHERSCHUN, L., LEE, M. W. & LIM, H. W. 2001. Diltiazem-associated photodistributed hyperpigmentation: a review of 4 cases. *Archives of dermatology,* 137**,** 179-182.

SCHIENER, R., BEHRENS-WILLIAMS, S. C., PILLEKAMP, H., PETER, R. U. & KERSCHER, M. 2001. Does the minimal phototoxic dose after 8-methoxypsoralen baths correlate with the individual's skin phototype? *Photodermatology, photoimmunology & photomedicine,* 17**,** 156-158.

SCHRÖDER, W., SOMMER, H., GLADSTONE, B. P., FOSCHI, F., HELLMAN, J., EVENGARD, B. & TACCONELLI, E. 2016. Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy,* 71**,** 1800-1806.

SCHUCH, A. P., MORENO, N. C., SCHUCH, N. J., MENCK, C. F. M. & GARCIA, C. C. M. 2017. Sunlight damage to cellular DNA: Focus on oxidatively generated lesions. *Free Radical Biology and Medicine,* 107**,** 110-124.

SCHUHWERK, M. & BEHRENS, R. H. 1998. Doxycycline as first line malarial prophylaxis: how safe is it? *Journal of travel medicine,* 5**,** 102-102.

SCHWARZ, T. & HALLIDAY, G. M. 2007. Photoimmunology. *BASIC AND CLINICAL DERMATOLOGY,* 38**,** 55.

SCHWARZE, H., ALBES, B., MARGUERY, M., LOCHE, F. & BAZEX, J. 1998a. Evaluation of drug-induced photosensitivity by UVB photopatch testing. *Contact dermatitis,* 39.

SCHWARZE, H., ALBES, B., MARGUERY, M., LOCHE, F. & BAZEX, J. 1998b. Evaluation of drug-induced photosensitivity by UVB photopatch testing. *Contact dermatitis,* 39**,** 200-200.

SEGGEV, J. S. & LAGSTEIN, Z. 1996. Photosensitivity skin reactions to calcium channel blockers. *Journal of allergy and clinical immunology,* 97**,** 852-855.

SEIDEMAN, P. & ROS, A. 1992. Sensitivity to UV light during treatment with chloroquine in rheumatoid arthritis. *Scandinavian journal of rheumatology,* 21**,** 245-247.

SEISHIMA, M., SHIBUYA, Y., KATO, G. & WATANABE, K. 2010. Photoleukomelanoderma possibly caused by etretinate in a patient with psoriasis. *Acta dermato-venereologica,* 90**,** 85-86.

SELVAAG, E. 1997. Clinical drug photosensitivity. A retrospective analysis of reports to the Norwegian Adverse Drug Reactions Committee from the years 1970–1994. *Photodermatology, photoimmunology & photomedicine,* 13**,** 21-23.

SELVAAG, E. & THUNE, P. 1997. Phototoxicity to sulphonamide-derived oral antidiabetics and diuretics: investigations in hairless mice. *Photodermatology, photoimmunology & photomedicine,* 13**,** 4-8.

SHAH, N. & WARNAKULASURIYA, S. 2004. Amiodarone-induced peri-oral photosensitivity. *Journal of oral pathology & medicine,* 33**,** 56-58.

SHAH, N. & ZAMBIDIS, E. T. 2009. False-photosensitivity and transient hemiparesis following high-dose intravenous and intrathecal methotrexate for treatment of acute lymphoblastic leukemia. *Pediatric blood & cancer,* 53**,** 103-105.

SHAHIN, M. H. & JOHNSON, J. A. 2016. Mechanisms and pharmacogenetic signals underlying thiazide diuretics blood pressure response. *Current opinion in pharmacology,* 27**,** 31-37.

SHANKS, G. D. 2016. Historical review: problematic malaria prophylaxis with quinine. *The American journal of tropical medicine and hygiene,* 95**,** 269-272.

SHARMA, A., BALDI, A. & SHARMA, D. K. 2017. Drug induced generalized skin eruption in a diabetes mellitus patient receiving a metformin plus simvastatin in a tertiary care teaching hospital in Punjab. *Curr Res Diabetes Obes J,* 4**,** 4-6.

SHARMA, V., GUPTA, V., JANGID, B. & PATHAK, M. 2018. Modification of the Fitzpatrick system of skin phototype classification for the Indian population, and its correlation with narrowband diffuse reflectance spectrophotometry. *Clinical and experimental dermatology,* 43**,** 274-280.

SHARP, M. T. & HORN, T. D. 2005. Pseudoporphyria induced by voriconazole. *Journal of the American Academy of Dermatology,* 53**,** 341-345.

SHELLEY, E. & SHELLEY, W. 1988. The subcorneal pustular drug eruption: an example induced by norfloxacin. *Cutis,* 42**,** 24-27.

SHELLEY, W., ELPERN, D. & SHELLEY, E. D. 1986. Naproxen photosensitization demonstrated by challenge. *Cutis,* 38**,** 169-170.

SHELLEY, W. B. & SHELLEY, E. D. 1992. A dermatologic diary. Portrait of a practice. *Cutis,* 49**,** 313.

SHELLEY, W. B., SHELLEY, E. D. & BURMEISTER, V. 1987. Argyria: the intradermal "photograph," a manifestation of passive photosensitivity. *Journal of the American Academy of Dermatology,* 16**,** 211-217.

SHEU, J., HAWRYLUK, E. B., GUO, D., LONDON, W. B. & HUANG, J. T. 2015. Voriconazole phototoxicity in children: a retrospective review. *Journal of the American Academy of Dermatology,* 72**,** 314-320.

SHUKLA, A., MAHAPATRA, A., GOGTAY, N. & KHOPKAR, U. 2010. Esomeprazole-induced photoallergic dermatitis. *Journal of postgraduate medicine,* 56**,** 229.

SICARI, M. C., LEBWOHL, M., BARAL, J., WEXLER, P., GORDON, R. E. & PHELPS, R. G. 1999. Photoinduced dermal pigmentation in patients taking tricyclic antidepressants: histology, electron microscopy, and energy dispersive spectroscopy. *Journal of the American Academy of Dermatology,* 40**,** 290-293.

SILVESTRE, J. F., ALBARES, M., CARNERO, L. & BOTELLA, R. 2001. Photodistributed felodipine-induced facial telangiectasia. *Journal of the American Academy of Dermatology,* 45**,** 323-324.

SINCLAIR, S. & DIFFEY, B. 1997. Sun protection provided by ladies stockings. *British Journal of Dermatology,* 136**,** 239-241.

SINGER, J. P., BOKER, A., METCHNIKOFF, C., BINSTOCK, M., BOETTGER, R., GOLDEN, J. A., GLIDDEN, D. V. & ARRON, S. T. 2012. High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients. *The Journal of heart and lung transplantation,* 31**,** 694-699.

SLINEY, D. H. & WENGRAITIS, S. 2006. Is a differentiated advice by season and region necessary? *Progress in biophysics and molecular biology,* 92**,** 150-160.

SOMMER, M., TRAUTMANN, A. & STOEVESANDT, J. 2015. Relief of photoallergy: atorvastatin replacing simvastatin. *Journal of investigational allergology & clinical immunology,* 25**,** 138-140.

SON, E.-A. & IUGAĬ, Z. 1992. A case of photodermatosis after long-term use of amiodarone. *Klinicheskaia meditsina,* 70**,** 46-46.

SPENCER, E., BRASSEY, J. & MAHTANI, K. 2017. Recall bias. *catalogue of bias*.

SPENCER, S., DARKE, C. & MURPHY, G. 1996. Hla-dr4 B1 0407-Strong Association With Actinic Prurigo In Ireland. *British Journal of Dermatology, Supplement,* 135**,** 65.

SPIELMANN, H., BALLS, M., BRAND, M., DÖRING, B., HOLZHÜTTER, H., KALWEIT, S., KLECAK, G., EPLATTENIER, H., LIEBSCH, M. & LOVELL, W. 1994. EEC/COLIPA project on in vitro phototoxicity testing: First results obtained with a Balb/c 3T3 cell phototoxicity assay. *Toxicology in vitro,* 8**,** 793-796.

SPIEWAK, R. 2010. Systemic photoallergy to terbinafine. *Allergy,* 65**,** 1071-1072.

SPIKES, J. D. 1989. Photosensitization. *The science of photobiology.* Springer.

SPIKES, J. D. 1998. Photosensitizing properties of quinine and synthetic antimalarials. *Journal of Photochemistry and Photobiology B: Biology,* 42**,** 1-11.

SRIVASTAVA, M., RENCIC, A., DIGLIO, G., SANTANA, H., BONITZ, P., WATSON, R., HA, E., ANHALT, G. J., PROVOST, T. T. & NOUSARI, C. H. 2003. Drug-induced, Ro/SSA-positive cutaneous lupus erythematosus. *Archives of dermatology,* 139**,** 45-49.

STAFFORD, R., FARRAR, M., KIFT, R., DURKIN, M., BERRY, J., WEBB, A. & RHODES, L. 2010. The impact of photosensitivity disorders on aspects of lifestyle. *British Journal of Dermatology,* 163**,** 817-822.

STANDARD, C. 1998. Erythema reference action spectrum and standard erythema dose. *CIE S,* 7**,** E1998.

STEDMAN, C. & BARCLAY, M. 2000. Comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. *Alimentary pharmacology & therapeutics,* 14**,** 963-978.

STENBERG, A. 1990. Pseudoporphyria and sunbeds. *Acta dermato-venereologica,* 70**,** 354-356.

STERN, R. S. 1998. Photocarcinogenicity of drugs. *Toxicology letters,* 102**,** 389-392.

STERN, R. S. & BIGBY, M. 1984. An expanded profile of cutaneous reactions to nonsteroidal anti-inflammatory drugs: reports to a specialty-based system for spontaneous reporting of adverse reactions to drugs. *JAMA,* 252**,** 1433-1437.

STIERNER, U., ROSDAHL, I., AUGUSTSSON, A. & KÅGEDAL, B. 1989. UVB irradiation induces melanocyte increase in both exposed and shielded human skin. *Journal of investigative dermatology,* 92**,** 561-564.

STORCK, H. 1965. Photoallergy and photosensitivity: Due to systemically administered drugs. *Archives of dermatology,* 91**,** 469-482.

STRATIGOS, A. J., ANTONIOU, C., PAPATHANAKOU, E., DABOUDI, M., TRANAKA, K., TSARA, K. & KATSAMBAS, A. D. 2003. Spectrum of idiopathic photodermatoses in a Mediterranean country. *International journal of dermatology,* 42**,** 449-454.

STRICKLAND, I., RHODES, L. E., FLANAGAN, B. F. & FRIEDMANN, P. S. 1997. TNF-α and IL-8 are upregulated in the epidermis of normal human skin after UVB exposure: correlation with neutrophil accumulation and E-selectin expression. *Journal of Investigative Dermatology,* 108**,** 763-768.

STRLE, F., CIMPERMAN, J., MARASPIN, V., LOTRIC-FURLAN, S. & RUŹIĆ-SABLJIĆ, E. 1996. Azithromycin and doxycycline for treatment ofBorrelia culture-positive erythema migrans. *Infection,* 24**,** 64-68.

SUAREZ, S. M., COHEN, P. R. & DELEO, V. A. 1990. Bullous photosensitivity to naproxen:"pseudoporphyria". *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* 33**,** 903-908.

SUSONG, J. & CARRIZALES, S. 2014. Lichenoid photosensitivity: an unusual reaction to doxycycline and an unusual response. *Cutis,* 93.

SUTHERLAND, J. C. & GRIFFIN, K. P. 1981. Absorption spectrum of DNA for wavelengths greater than 300 nm. *Radiation research,* 86**,** 399-410.

TAKEICHI, S., KUBO, Y., ARASE, S., HASHIMOTO, T. & ANSAI, S.-I. 2009. Brunsting-Perry type localized bullous pemphigoid, possibly induced by furosemide administration and sun exposure. *European Journal of Dermatology,* 19**,** 500-503.

TAMAT, S. R. & MOORE, D. E. 1983. Photolytic decomposition of hydrochlorothiazide. *Journal of pharmaceutical sciences,* 72**,** 180-183.

TAN, C. K. & YAP, K. B. 2018. Tamsulosin-induced photosensitivity rash. *Singapore medical journal,* 59**,** 336.

TAN, S., BERTH-JONES, J. & BURNS, D. 1989. Lichen planus and photo-onycholoysis induced by quinine. *Clinical and experimental dermatology,* 14**,** 335-335.

TANAKA, N., KAWADA, A., OHNISHI, Y., HIRUMA, M. & TAJIMA, S. 1997. Photosensitivity due to doxycycline hydrochloride with an unusual flare. *Contact Dermatitis,* 37**,** 93-94.

TANIGUCHI, S. & HAMADA, T. 1996. Photosensitivity and thrornbocytopenia due to amitriptyline. *American journal of hematology,* 53**,** 49-50.

TASHKENT, Y. & AIYAPPAN, V. 2018. Lesson of the month 2: An unusual adverse reaction associated with pramipexole. *Clinical Medicine,* 18**,** 259.

TAYLOR, S. C., ARSONNAUD, S. & CZERNIELEWSKI, J. 2005. The Taylor Hyperpigmentation Scale: a new visual assessment tool for the evaluation of skin color and pigmentation. *CUTIS-NEW YORK-,* 76**,** 270.

TERAMURA, T., MIZUNO, M., ASANO, H., NAITO, N., ARAKANE, K. & MIYACHI, Y. 2012. Relationship between sun-protection factor and application thickness in high-performance sunscreen: double application of sunscreen is recommended. *Clinical and Experimental Dermatology: Experimental dermatology,* 37**,** 904-908.

THAKUR, V., BAKSHI, S. & BISHNOI, A. 2020. Adalimumab-induced photosensitivity and oral erosions in rheumatoid arthritis. *Postgraduate Medical Journal*.

THALMANN, H. & MÜLLER, J. 2009. Suspected borreliosis: therapy is incompatible with the French sun. *MMW Fortschritte der Medizin,* 151**,** 5-5.

THAMI, G., KAUR, S. & KANWAR, A. 2002. Delayed reactivation of haloperidol induced photosensitive dermatitis by methotrexate. *Postgraduate medical journal,* 78**,** 116-117.

THOMAS, R. M. & MUNRO, D. 1986. Lichen planus in a photosensitive distribution due to quinine. *Clinical and experimental dermatology,* 11**,** 97-101.

THUAL, N., PENVEN, K., CHEVALLIER, J., DOMPMARTIN, A. & LEROY, D. Fluvastatin-induced dermatomyositis. Annales de dermatologie et de venereologie, 2005. 996-999.

THUNE, P., JANSEN, C., WENNERSTEN, G., RYSTEDT, I., BRODTHAGEN, H. & MCFADDEN, N. 1988. The Scandinavian multicenter photopatch study 1980-1985. *Photo-dermatology,* 5**,** 261-269.

TODD, P., NORRIS, P., HAWK, J. & DU VIVIER, A. 1995. Ranitidine-induced photosensitivity. *Clinical and experimental dermatology,* 20**,** 146-148.

TOKURA, Y., IWAMOTO, Y., MIZUTANI, K. & TAKIGAWA, M. 1996a. Sparfloxacin phototoxicity: potential photoaugmentation by ultraviolet A and B sources. *Archives of dermatological research,* 288**,** 45-50.

TOKURA, Y., NISHIJIMA, T., YAGI, H., FURUKAWA, F. & TAKIGAWA, M. 1996b. Photohaptenic properties of fluoroquinolones. *Photochemistry and photobiology,* 64**,** 838-844.

TOLLAND, J., MCKEOWN, P. & CORBETT, J. 2007. Voriconazole-induced pseudoporphyria. *Photodermatology, photoimmunology & photomedicine,* 23**,** 29-31.

TOMS-WHITTLE, L., JOHN, L. & BUCKLEY, D. 2011. Drug-induced subacute cutaneous lupus erythematosus associated with omeprazole. *Clinical and experimental dermatology,* 36**,** 281-283.

TORINUKI, W. 1980. Photosensitivity due to hydrochlorothiazide. *The Journal of dermatology,* 7**,** 293-296.

TRAKATELLI, M., BYLAITE-BUCINSKIENE, M., CORREIA, O., COZZIO, A., DE VRIES, E., MEDENICA, L., NAGORE, E., PAOLI, J., STRATIGOS, A. J. & DEL MARMOL, V. 2017. Clinical assessment of skin phototypes: watch your words! *European Journal of Dermatology,* 27**,** 615-619.

TRAKATELLI, M., CHARALAMPIDIS, S., NOVAKOVIC, L., PATSATSI, A., KALABALIKIS, D. & SOTIRIADIS, D. 2009. Photodermatoses with onset in the elderly. *British Journal of Dermatology,* 161**,** 69-77.

TRAYNOR, N., BARRATT, M., LOVELL, W., FERGUSON, J. & GIBBS, N. 2000. Comparison of an in vitro cellular phototoxicity model against controlled clinical trials of fluoroquinolone skin phototoxicity. *Toxicology in vitro,* 14**,** 275-283.

TREESIRICHOD, A., CHANSAKULPORN, S. & WATTANAPAN, P. 2014. Correlation between skin color evaluation by skin color scale chart and narrowband reflectance spectrophotometer. *Indian journal of dermatology,* 59**,** 339.

TRIBÓ, M. J., TURROJA, M., CASTAÑO-VINYALS, G., BULBENA, A., ROS, E., GARCÍA-MARTÍNEZ, P., TAUSK, F., SAGRISTÀ, M., PUJOL, R. M. & FERRAN, M. 2019. Patients with moderate to severe psoriasis associate with higher risk of depression and anxiety symptoms: results of a multivariate study of 300 Spanish individuals with psoriasis. *Acta Dermato-Venereologica,* 99**,** 417-422.

TSAI, K. C., YANG, J. H. & HUNG, S. J. 2017. Fenofibrate-induced photosensitivity–a case series and literature review. *Photodermatology, photoimmunology & photomedicine,* 33**,** 213-219.

TUCHINDA, C., SRIVANNABOON, S. & LIM, H. W. 2006. Photoprotection by window glass, automobile glass, and sunglasses. *Journal of the American Academy of Dermatology,* 54**,** 845-854.

URBACH, F. 1997. Phototoxicity and possible enhancement of photocarcinogenesis by fluorinated quinolone antibiotics. *Journal of Photochemistry and Photobiology B: Biology,* 37**,** 169-170.

VACCARO, M., BORGIA, F., BARBUZZA, O. & GUARNERI, B. 2007. Photodistributed eruptive telangiectasia: an uncommon adverse drug reaction to venlafaxine. *British Journal of Dermatology,* 157**,** 822-824.

VAILLANT, L., LE MARCHAND, D., GROGNARD, C., HOCINE, R. & LORETTE, G. 1988. Photosensitivity to methyldopa. *Archives of dermatology,* 124**,** 326-327.

VAN DER HEIJDEN, P. G., VAN PUIJENBROEK, E. P., VAN BUUREN, S. & VAN DER HOFSTEDE, J. W. 2002. On the assessment of adverse drug reactions from spontaneous reporting systems: the influence of under-reporting on odds ratios. *Statistics in medicine,* 21**,** 2027-2044.

VAN HASSELT, J. G., VAN EIJKELENBURG, N. K., HUITEMA, A. D., SCHELLENS, J. H. & SCHOUTEN-VAN MEETEREN, A. Y. 2013. Severe skin toxicity in pediatric oncology patients treated with voriconazole and concomitant methotrexate. *Antimicrobial agents and chemotherapy,* 57**,** 2878-2881.

VAN WAUWE, J., COENE, M., GOOSSENS, J., COOLS, W. & MONBALIU, J. 1990. Effects of cytochrome P-450 inhibitors on the in vivo metabolism of all-trans-retinoic acid in rats. *Journal of Pharmacology and Experimental Therapeutics,* 252**,** 365-369.

VAN WEELDEN, H., BOLLING, H. H., DE LA FAILLE, H. B. & VAN DER LEUN, J. C. 1982. Photosensitivity caused by chloroquine. *Archives of Dermatology,* 118**,** 290-290.

VASSILEVA, S. G., MATEEV, G. & PARISH, L. C. 1998a. Antimicrobial photosensitive reactions. *Archives of internal medicine,* 158**,** 1993-2000.

VASSILEVA, S. G., MATEEV, G. & PARISH, L. C. J. A. O. I. M. 1998b. Antimicrobial photosensitive reactions. 158**,** 1993-2000.

VELUŠČEK, M., BAJROVIĆ, F. F., STRLE, F. & STUPICA, D. 2018. Doxycycline-induced photosensitivity in patients treated for erythema migrans. *BMC infectious diseases,* 18**,** 365.

VERDEL, B., SOUVEREIN, P., MEYBOOM, R., KARDAUN, S., LEUFKENS, H. & EGBERTS, A. 2009. Risk of drug-induced photosensitivity: focus on spectroscopic and molecular characteristics. *Pharmacoepidemiology and drug safety,* 18**,** 602-609.

VERMA, R., VASUDEVAN, B., SHANKAR, S., PRAGASAM, V., SUWAL, B. & VENUGOPAL, R. 2012. First reported case of tenofovir-induced photoallergic reaction. *Indian journal of pharmacology,* 44**,** 651.

VILA, M. S., VALDÉS, V. M., MARCOS, J. B. & BADAL, J. A. 1985. Intense photodermatosis due to amiodarone. *Medicina clinica,* 84**,** 379-379.

VILAPLANA, J., BOTEY, E., LECHA, M., HERRERO, C. & ROMAGUERA, C. 2002. Photosensitivity induced by paroxetine. *Contact dermatitis,* 47**,** 109-125.

VINKS, S. T., HEIJERMAN, H. M., DE JONGE, P. & BAKKER, W. 1993. Photosensitivity due to ambulatory intravenous ceftazidime in cystic fibrosis patient. *The Lancet,* 341**,** 1221-1222.

VIOLA, E., PITTONI, A. C., DRAHOS, A., MORETTI, U. & CONFORTI, A. 2015. Photosensitivity with angiotensin II receptor blockers: a retrospective study using data from VigiBase®. *Drug safety,* 38**,** 889-894.

WADHWANI, A., SHARMA, V., RAMAM, M. & KHAITAN, B. 2013. A clinical study of the spectrum of photodermatoses in dark-skinned populations. *Clinical and experimental dermatology,* 38**,** 823-829.

WAGNER, G., DIFFEY, B. & IVE, F. 1994. 'I'll have mine with a twist of lemon'. Quinine photosensitivity from excessive intake of tonic water. *British Journal of Dermatology,* 131**,** 734-735.

WAGNER, S., WELKE, F. & GOOS, M. 2000. Occupational UVA-induced allergic photodermatitis in a welder due to hydrochlorothiazide and ramipril. *Contact dermatitis,* 43**,** 245-246.

WAHLBERG, J. E. & BOMAN, A. 1981. Contact sensitivity to quinidine sulfate from occupational exposure. *Contact Dermatitis,* 7**,** 27-31.

WAITZER, S., BUTANY, J., FROM, L., HANNA, W., RAMSAY, C. & DOWNAR, E. 1987. Cutaneous ultrastructural changes and photosensitivity associated with amiodarone therapy. *Journal of the American Academy of Dermatology,* 16**,** 779-787.

WALBURN, J. & SARKANY, R. P. 2020. Quality of life in the photodermatoses: the hidden toll of photosensitivity. *British Journal of Dermatology,* 182**,** 1077-1077.

WALLEY, T., DUGGAN, A. K., HAYCOX, A. R. & NIZIOL, C. J. 2003. Treatment for newly diagnosed hypertension: patterns of prescribing and antihypertensive effectiveness in the UK. *Journal of the Royal Society of Medicine,* 96**,** 525-531.

WALTER-RYAN, W. G., KERN, E. E., SHIRRIFF, J. R. & THOMAS, J. M. 1985. Persistent photoaggravated cutaneous eruption induced by imipramine. *JAMA,* 254**,** 357-358.

WALTER, J. F., BRADNER, H. & CURTIS, G. P. 1984. Amiodarone photosensitivity. *Archives of dermatology,* 120**,** 1591-1594.

WANG, S. Q., KOPF, A. W., MARX, J., BOGDAN, A., POLSKY, D. & BART, R. S. 2001. Reduction of ultraviolet transmission through cotton T-shirt fabrics with low ultraviolet protection by various laundering methods and dyeing: clinical implications. *Journal of the American Academy of Dermatology,* 44**,** 767-774.

WARD, M. M. 2013. Estimating disease prevalence and incidence using administrative data: some assembly required. The Journal of Rheumatology.

WARE, O. R., DAWSON, J. E., SHINOHARA, M. M. & TAYLOR, S. C. 2020. Racial limitations of Fitzpatrick skin type. *Cutis.,* 105**,** 77-80.

WEISS, S. R., LIM, H. W. & CURTIS, G. 1984. Slate-gray pigmentation of sun-exposed skin induced by amiodarone. *Journal of the American Academy of Dermatology,* 11**,** 898-900.

WESTWICK, T., SHERERTZ, E., MCCARLEY, D. & FLOWERS, F. 1987. Delayed reactivation of sunburn by methotrexate: sparing of chronically sun-exposed skin. *Cutis,* 39**,** 49-51.

WETTER, D. A. & DAVIS, M. D. Lupus-Like Syndrome Attributable to Anti—Tumor Necrosis Factor α Therapy in 14 Patients During an 8-Year Period at Mayo Clinic. Mayo clinic proceedings, 2009. Elsevier, 979-984.

WHITCOMBE, D. M., CARTER, N. P., ALBERTSON, D. G., SMITH, S. J., RHODES, D. A. & COX, T. M. 1991. Assignment of the human ferrochelatase gene (FECH) and a locus for protoporphyria to chromosome 18q22. *Genomics,* 11**,** 1152-1154.

WHITE, I. R. 1983. Photopatch test in a hydrochlorothiazide drug eruption. *Contact Dermatitis,* 9**,** 237.

WILKINSON, S., DOUGLAS, I., STIRNADEL-FARRANT, H., FOGARTY, D., POKRAJAC, A., SMEETH, L. & TOMLINSON, L. 2018. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. *BMJ open,* 8**,** e022768.

WILLIS, I. & EARLES, R. 2005. A new skin classification system relevant to people of African descent. *COSMETIC DERMATOLOGY-CEDAR KNOLLS-,* 18**,** 209-226.

WITTAL, R. A., FISCHER, G. O., GEORGOURAS, K. E. & BAIRD, P. J. 1992. Skin reactions to diltiazem. *Australasian journal of dermatology,* 33**,** 11-18.

WLODEK, C. & NARAYAN, S. 2014. A reminder about photo-onycholysis induced by tetracycline, and the first report of a case induced by lymecycline. *Clinical and experimental dermatology,* 6**,** 746-747.

WOLF, R., DORFMAN, B. & KRAKOWSKI, A. 1987. Quinidine-induced lichenoid and eczematous photodermatitis. *Dermatology,* 174**,** 285-289.

WONG, S. & KHOO, L. 2005. Analysis of photodermatoses seen in a predominantly Asian population at a photodermatology clinic in Singapore. *Photodermatology, photoimmunology & photomedicine,* 21**,** 40-44.

WONG, S. X., THAM, M. Y., GOH, C. L., CHEONG, H. H. & CHAN, S. Y. 2019. Spontaneous cutaneous adverse drug reaction reports—An analysis of a 10-year dataset in Singapore. *Pharmacology research & perspectives,* 7**,** e00469.

WOOLLONS, A., CLINGEN, P., PRICE, M., FARLETT, C. & GREEN, M. 1997. Induction of mutagenic DNA damage in human fibroblasts after exposure to artificial tanning lamps. *British Journal of Dermatology,* 137**,** 687-692.

WULF, H. C., PHILIPSEN, P. A. & RAVNBAK, M. H. 2010. Minimal erythema dose and minimal melanogenesis dose relate better to objectively measured skin type than to Fitzpatricks skin type. *Photodermatology, photoimmunology & photomedicine,* 26**,** 280-284.

YANAMANDRA, U., SAHU, K. K., MALHOTRA, P. & VARMA, S. 2014. Photodermatosis secondary to hydroxyurea. *Case Reports,* 2014**,** bcr2014205974.

YAP, L. M., FOLEY, P. A., CROUCH, R. B. & BAKER, C. S. 2000. Drug-induced solar urticaria due to tetracycline. *Australasian journal of dermatology,* 41**,** 181-184.

YASUDA, S., MIZUNO, N., KAWABE, Y. & SAKAKIBARA, S. 1988. Photosensitive lichenoid reaction accompanied by nonphotosensitive subacute prurigo caused by carbamazepine. *Photo-dermatology,* 5**,** 206-210.

YAZICI, A. C., BAZ, K., IKIZOGLU, G., KOKTURK, A., UZUMLU, H. & TATAROGLU, C. 2004. Celecoxib-induced photoallergic drug eruption. *International journal of dermatology,* 43**,** 459-461.

YOKOTE, R., TOKURA, Y., IGARASHI, N., ISHIKAWA, O. & MIYACHI, Y. 1998. Photosensitive drug eruption induced by flutamide. *European journal of dermatology: EJD,* 8**,** 427.

YONES, S., O'DONOGHUE, N., PALMER, R., MENAGÉ, H. D. P. & HAWK, J. 2005. Persistent severe amiodarone-induced photosensitivity. *Clinical and Experimental Dermatology: Clinical dermatology,* 30**,** 500-502.

YONG, C. K., PRENDIVILLE, J., PEACOCK, D. L., WONG, L. T. & DAVIDSON, A. G. F. 2000. An unusual presentation of doxycycline-induced photosensitivity. *Pediatrics,* 106**,** e13-e13.

YOUNG, A. R. 1997. Chromophores in human skin. *Physics in Medicine and Biology,* 42**,** 789.

YOUNG, A. R., POTTEN, C. S., CHADWICK, C. A., MURPHY, G. M., HAWK, J. L. & COHEN, A. J. 1991. Photoprotection and 5-MOP photochemoprotection from UVR-induced DNA damage in humans: the role of skin type. *Journal of investigative dermatology,* 97**,** 942-948.

YOUNG, L., SHEHADE, S. & CHALMERS, R. 1990. Cutaneous reactions to diltiazem. *Clinical and experimental dermatology,* 15**,** 467.

ZACHARY, C., SLATER, D., HOLT, D., STOREY, G. & MACDONALD, D. 1984. The pathogenesis of amiodarone-induced pigmentation and photosensitivity. *British Journal of Dermatology,* 110**,** 451-456.

ZENAROLA, P., GATTI, S. & LOMUTO, M. 1991. Photodermatitis due to nifedipine: report of 2 cases. *Dermatology,* 182**,** 196-198.

ZHOU, W. & MOORE, D. E. 1997. Photosensitizing activity of the anti-bacterial drugs sulfamethoxazole and trimethoprim. *Journal of Photochemistry and Photobiology B: Biology,* 39**,** 63-72.

ZIEGLER, A., JONASON, A. S., LEFFELLT, D. J., SIMON, J. A., SHARMA, H. W., KIMMELMAN, J., REMINGTON, L., JACKS, T. & BRASH, D. E. 1994. Sunburn and p53 in the onset of skin cancer. *Nature,* 372**,** 773-776.

Appendix 1

Summary of published quinine photosensitivity reports

Clinical presentation	Age	Sex	No of cases	Drugs	References
Photodistributed eruption and eczematous reaction (photoallergic reaction)	72	F	1	Quinine hydrochloride	(Ljunggren and Sjövall, 1986)
Psoriasis patient developed photosensitivity and a Koebner reaction whilst receiving phototherapy	41	F	1	Quinine	(Guzzo and Kaidbey, 1990)
Occupational photodermatitis (photoallergy reaction)	NA	NA	1	Quinine sulphate	(Jeanmougin et al., 1984)
Photodistributed maculopapular vesicles (photoallergy reaction)	38	F	1	Quinine	(Nacher et al., 2005)
Photodistributed lichenoid drug eruption	76	M	1	Quinine sulfate	(Natkunarajah et al., 2010a)
Photosensitive lichenoid eruption	62 - 78	F	5	Quinine sulphate	(Dawson, 1986)
Lichen planus and photo-onycholysis	66	M	1	Quinine sulphate	(Tan et al., 1989)
Photodistributed lichenoid drug eruption	78	M	1	Quinidine	(Thomas and Munro, 1986)
Photodistributed lichenoid drug eruption	61	F	1	Quinidine	(Sarkany, 1967)
Photosensitive dermatitis	NA	NA	3	Quinidine sulfate	(Pariser and Taylor, 1975)
Cutaneous photosensitivity Pruritic and burning oedematous erythema) (3cases). Lichen planus (one case)	69–83	3 F 1 M	4	Quinine sulphate	(Ferguson et al., 1987)
Photoallergic reaction	78	M	1	Quinine sulphate	(Hickey et al., 2007)
Photosensitivity from excessive intake of tonic water	59	F	1	Quinine hydrochloride	(Wagner et al., 1994)
Photocontact contact allergy	75	M	1	Quinine	(Liunggren et al., 1992)

Clinical presentation	Age	Sex	No of cases	Drugs	References
Photodistributed eczema and oedema	69–84	2 F 1 M	3	Quinine sulphate	(Diffey et al., 1988)
Histological features similar to mycosis fungoides	75	F	1	Quinine gluconate	(Okun et al., 1994)
Contact dermatitis	26,27,52	M	3	Quinidine sulfate	(Wahlberg and Boman, 1981)
Photocontact contact allergy and telangiectasia	50	F	1	Quinidine	(Calnan, 1978)

Appendix 2

Summary of published thiazide diuretic photosensitivity reports

Clinical presentation	Age	Sex	No of cases	Drug	References
Photodistributed erythema & papulosquamous eruptions	70	F	1	Altizide (thiazide diuretic)	(Schwarze et al., 1998b)
Acute eczematous reaction	68	M	1	Hydrochlorothiazide	(White, 1983)
Lichenoid eruptions (hydrochlorothiazide) Vesicular eruption (chlorothiazide)	60	F	3	Hydrochlorothiazide Chlorothiazide	(Harber et al., 1959b)
Lichen planus	77	M	1	Hydrochlorothiazide	(Johnston and Coulson, 2002)
Petechial rash	78	F	1	Chlorothiazide	(NORINS, 1959)
Chronic Eczematous reaction & persistent photosensitivity	44–68	2 F 2 M	4	Hydrochlorothiazide	(Robinson et al., 1985)
Pseudoporphyria in areas affected by vitiligo	65	M	1	Hydrochlorothiazide	(Motley, 1990)
Acute dermatitis	68	M	1	Hydrochlorothiazide	(Fernández de Cores et al., 1987)
Photoleukomelanoderma	68	M	1	Hydrochlorothiazide	(Masuoka et al., 2011)
Photo-onycholysis	75	F	1	Indapamide	(Rutherford and Sinclair, 2007)
SLCE	42–68	4 M 1 F	5	Hydrochlorothiazide	(Reed et al., 1985c)

Clinical presentation	Age	Sex	No of cases	Drug	References
SLCE	61–75	2 F 1 M	3	Hydrochlorothiazide	(Darken and McBurney, 1988)
SLCE	64	F	1	Hydrochlorothiazide	(Parodi et al., 1989)
SLCE	65	M	1	Hydrochlorothiazide	(Brown and Deng, 1995)
Photodistributed erythema in all cases. SCLE in two cases	44–65	4 M 1 F	5	Hydrochlorothiazide	(Srivastava et al., 2003)
Sunburn-like eruptions	NA	NA	1	Hydrochlorothiazide	(Torinuki, 1980)
Photodistributed erythema in most patients & SCLE-like eruption in one patient	42–75	21 F 12 M	33	Thiazide: 14 patients; thiazide & photoactive drugs:7 patients; thiazide & non-photoactive drugs:12 patients	(Addo et al., 1987)

Appendix 3

Summary of published voriconazole photosensitivity reports

Clinical presentation	Age	Sex	No of cases	Drug	References
Photodistributed erythema with superimposed blistering	11,13	M	2	Voriconazole	(Rubenstein et al., 2004)
Photodistributed erythema and macular eruption	50	M	1	Voriconazole	(Malani and Aronoff, 2008)
Pseudoporphyria	55,53, 65	1 F 2 M	3 studies	Voriconazole	(Dolan et al., 2004, Sharp and Horn, 2005, Tolland et al., 2007)
Bullous phototoxicity (painful blisters)	37	F	1	Voriconazole	(Barbosa and Wetter, 2014)
Desquamation of skin and cheilitis	65	M	1	Voriconazole	(Hickman et al., 2010)
Phototoxic reaction	11-86	40 F 47 M	87	Voriconazole	(Sheu et al., 2015)
Toxic epidermal necrolysis	39,81	1 M 1 F	2	Voriconazole	(Curigliano et al., 2006, Huang et al., 2004)
Facial erythema and cheilitis (4 cases). Discoid lupus erythematosus-like lesions (one case)	38–55	2 F 3 M	5	Voriconazole	(Denning and Griffiths, 2001)
Post allogeneic bone marrow transplantation who developed blistering eruptions	19,45	1 M 1 F	2	Voriconazole	(Conlon et al., 2008)

Clinical presentation	Age	Sex	No of cases	Drug	References
Photosensitivity in immunosuppressed patients	17–67	5 F 2 M	7	Voriconazole	(Auffret et al., 2006)
Multifocal squamous cell carcinomas in an HIV-infected patient	49	M	1	Voriconazole	(Brunel et al., 2008)
Photosensitivity cystic fibrosis patients	7–18	2 M 3 F	5	Voriconazole	(Cheng et al., 2010)
Photosensitivity reaction and skin peeling	47	M	1	Voriconazole	(Cortez et al., 2003)
Phototoxic skin reactions, cheilitis (2 cases) only, blisters formation (one patient)	4–8	NA	1	Voriconazole	(Bernhard et al., 2012)

Appendix 4

Summary of published PPI photosensitivity reports

Clinical presentation	Age	Sex	No of cases	Drug	References
SCLE	69	F	1	Esomeprazole	(Gliem et al., 2017a)
SCLE	74	F	1	Esomeprazole	(Alcántara-González et al., 2011)
SCLE	69 & 63	F	2	Lansoprazole	(Bracke et al., 2005b)
SCLE	60	F	1	Omeprazole	(Mankia et al., 2010)
SCLE	78 & 85	F	2	Omeprazole	(Toms-Whittle et al., 2011)
SCLE	61	F	1	Lansoprazole	(Panting et al., 2009)
Phototoxic dermatitis & discoid lupus	73	F	1	Pantoprazole	(Correia et al., 2001)
SCLE	63 & 69	F	2	Lansoprazole	(Bracke et al., 2005b)
SCLE	63 & 51 57 61 50	F M F F	5	Pantoprazole Lansoprazole Lansoprazole Omeprazole	(Dam and Bygum, 2008)
SCLE	60	F	1	Omeprazole	(Hung et al., 2015)
SCLE	30 31	M F	2	Pantoprazole Esomeprazole	(Almebayadh et al., 2013)
Photoallergic dermatitis	58	F	1	Esomeprazole	(Shukla et al., 2010)

Appendix 5

Medicines taken by the study participants and any clinical references describing photosensitive/phototoxic responses that were found

Drug name	Reference
Acenocoumarol	No cases found
Acetazolamide	No cases found
Acyclovir	(Rodriguez-Serna et al., 1999)
Adalimumab	(Thakur et al., 2020)
Aldomin (alpha methyldopa sesquihydrate)	No cases found
Alendronic acid	No cases found
Alfuzosin	No cases found
Allopurinol	No cases found
Alogliptin	No cases found
Amiodarone	(Chalmers et al., 1982, Harris et al., 1983, Walter et al., 1984, Weiss et al., 1984, Zachary et al., 1984, Ferguson et al., 1985, Vila et al., 1985, Boyle, 1986, Ferguson, 1986, Roupe et al., 1987, Waitzer et al., 1987, Rappersberger et al., 1989, Monk, 1990, Son and Iugaĭ, 1992, Shah and Warnakulasuriya, 2004, Reĭngardene and Zhilene, 2005, Yones et al., 2005, Gonzalez-Arriagada et al., 2013)
Amitriptyline	(Taniguchi and Hamada, 1996)
Amlodipine	(Grabczynska and Cowley, 2000, Erbagci, 2004, Byun et al., 2011, Rojas Mora et al., 2017, Bakkour et al., 2013, Cooper and Wojnarowska, 2003, Basarab et al., 1997)
Anagliptin	No cases found
Apixaban	No cases found
Arcoxia	No cases found
Aripiprazole	(Gregoriou et al., 2008)
Aspirin	No cases found
Atenolol	No cases found

Drug name	Reference
Atorvastatin	(Marguery et al., 2006, Korzeniowska et al., 2019)
Azathioprine	(Hofbauer et al., 2012, Perrett et al., 2008, Baadsgaard, 1986)
Azithromycin	No cases found
Bendroflumethiazide	(Diffey and Langtry, 1989)
Benzathine	No cases found
Benzthiazide	no cases found
Betahistine	No cases found
Bioflavonoids	No cases found
Bisacodyl	No cases found
Bisoprolol	No cases found
Bisphosphonate	No cases found
Bosentan	No cases found
Budesonide	No cases found
Bumetanide	No cases found
Buprenorphine	No cases found
Buscopan	No cases found
Calcium carbonate	No cases found
Calcium carbonate with cholecalciferol	No cases found
Canagliflozin	No cases found
Candesartan	(Viola et al., 2015)
carbamazepine	(Yasuda et al., 1988)
Carbatrol	No cases found
Carbocisteine	No cases found
Cetirizine	No cases found
Chlorphenamine	No cases found
Cholecalciferol	No cases found
Citalopram	(I˚ nalöz et al., 2001, Mecca et al., 2004, Röhrs et al., 2012, Ram-Wolf et al., 2008, Richard et al., 2001)

Drug name	Reference
Colesevelam	No cases found
Clonazepam	No cases found
Clonidine	No cases found
Clopidogrel	(Dogra and Kanwar, 2003)
Codeine	No cases found
Codeine and paracetamol	No cases found
Copaxone	No cases found
Cyclizine	No cases found
Dalteparin	No cases found
Diazepam	No cases found
Diclofenac	(Al-Kathiri and Al-Asmaili, 2016, Akat, 2013, Montoro et al., 2003, Fernández-Jorge et al., 2009, Kowalzick and Ziegler, 2006, Goday Bujan et al., 2001, O'Reilly et al., 1999, Le Corre et al., 1992)
Digoxin	No cases found
Dihydrocodeine and paracetamol	No cases found
Diltiazem	(Jaka et al., 2011, Desai et al., 2010, Kubo et al., 2010, Hanson and Petronic-Rosic, 2008, Ramírez et al., 2007, Boyer et al., 2003a, Scherschun et al., 2001, Young et al., 1990)
Disulfiram	No cases found
Docusate	No cases found
Donepezil	No cases found
Doxazosin	No cases found
Doxycycline	(Velušček et al., 2018, Layton and Cunliffe, 1993, Habif, 2006, Kuznetsov et al., 2011, Bishnoi and Vinay, 2019, Passier et al., 2004, Pazzaglia et al., 2014, Yong et al., 2000, Rabar et al., 2004, Susong and Carrizales, 2014, Lim and Triscott, 2003, Baxter et al., 2002, Luger et al., 1995, Lim and Murphy, 2003, Bjellerup and Ljunggren, 1994, Nguyen and Krakowski, 2016, Nowakowski et al., 1995, Tanaka et al., 1997, Ogrinc et al., 2006, Strle et al., 1996, Hafiji and Batchelor, 2010, Kus et al., 2005,

Drug name	Reference
	Schuhwerk and Behrens, 1998, Thalmann and Müller, 2009)
Dronedarone	(Ladizinski and Elpern, 2013, Kuo et al., 2014, Datar et al., 2019)
Duloxetine	No cases found
Dulaglutide	No cases found
Empagliflozin	No cases found
Emtricitabine/rilpivirine	(Verma et al., 2012)
Enalapril	(Kanwar et al., 1993b, O'Reilly et al., 1999, Sánchez-Borges and González-Aveledo, 2011, Shelley and Shelley, 1992)
Escitalopram	(Ram-Wolf et al., 2008)
Esomeprazole	(Shukla et al., 2010)
Estradiol	(Barton and Edwards, 2016, Horkay et al., 1975)
Etanercept	No cases found
Etodolac	No cases found
Exemestane	No cases found
Ezetimibe	No cases found
Felodipine	(Silvestre et al., 2001)
Fenofibrate	(Mohammed et al., 2017, Tsai et al., 2017, Kuwatsuka et al., 2016, Machet et al., 1997, Leroy et al., 1997, Leenutaphong and Manuskiatti, 1996, Gardeazabal et al., 1993, Leroy et al., 1990)
Fentanyl	No cases found
Fexofenadine	No cases found
Finasteride	No cases found
Flecainide	No cases found
Fluoxetine	(Pazzagli et al., 1998, Gaufberg and Ellison, 1995b)
Fluvastatin	(Thual et al., 2005)
Folic acid	No cases found
Forceval	No cases found

Drug name	Reference
Fortamind	No cases found
Furosemide	(Anderson et al., 1985, Heydenreich et al., 1977, Takeichi et al., 2009, Burry and Lawrence, 1976)
Gabapentin	No cases found
Gaviscon	No cases found
Gliclazide	No cases found
Glimepiride	No cases found
Glipizide	No cases found
Glucosamine	No cases found
Glyceryl trinitrate	No cases found
Green Tea	No cases found
Heparin	No cases found
Hydrochlorothiazide	(Rosenthal and Herrmann, 2019, Korzeniowska et al., 2019, Gómez-Bernal et al., 2014, Nakao et al., 2017, Masuoka et al., 2011, Friedman et al., 2012, Costagliola et al., 2008, Johnston and Coulson, 2002, Wagner et al., 2000, Diffey and Langtry, 1989, Halevy et al., 1986, Reed et al., 1985a, Robinson et al., 1985, Torinuki, 1980, Burckhardt and Sutter, 1963, Harber et al., 1959b, Harber et al., 1959a)
Hydrocortisone	No cases found
Hydroquinone	(Coulson, 1993, Olumide, 1987)
Hydroxycarbamide/hydroxyurea	(Yanamandra et al., 2014, León-Mateos et al., 2007)
Hydroxychloroquine	(Lisi et al., 2004, Metayer et al., 2001, Seideman and Ros, 1992, Baler, 1976)
Hydroxyzine	No cases found
Ibuprofen	(Bergner and Przybilla, 1992)
Indapamide	(Rutherford and Sinclair, 2007)
Infliximab	(Wetter and Davis, 2009)
Insulin	No cases found

Drug name	Reference
Irbesartan	(Viola et al., 2015, Korzeniowska et al., 2019)
Isosorbide Mononitrate	No cases found
Ivabradine	No cases found
Lactulose	No cases found
Lamotrigine	(Huang et al., 2010)
Lansoprazole	No cases found
Latanoprost	No cases found
Lercanidipine	No cases found
Letrozole	No cases found
Levetiracetam	No cases found
Levothyroxine	No cases found
Linagliptin	No cases found
Liraglutide	No cases found
Lisinopril	No cases found
Loperamide	No cases found
Loratadine	No cases found
Losartan	(Nakao et al., 2017, Viola et al., 2015, Shelley and Shelley, 1992)
Lymecycline	(Wlodek and Narayan, 2014)
Macrogol	No cases found
Mefenamic acid	(O'Reilly et al., 1999)
Memantine	No cases found
Mepolizumab	No cases found
Mesalazine	(Cozzani et al., 2014, Al-Niaimi and Calum, 2011, Horiuchi and Shimakura, 1999b)
Metformin	(Kastalli et al., 2009, Korzeniowska et al., 2019, Nakatani et al., 2012, Sharma et al., 2017)
Methotrexate	(Hoffmann et al., 2015, Kocatürk et al., 2014, Fernández et al., 2012, Shah and Zambidis, 2009, Khan et al., 2000, Westwick et al., 1987, Mallory and Berry, 1986, Neiman and Fye, 1985)
Metoclopramide	No cases found

Drug name	Reference
Metoprolol tartrate	No cases found
Mirabegron	No cases found
Mirtazapine	(Mendhekar and Inamdar, 2009)
Montelukast	No cases found
Morphine	No cases found
Mycophenolate	(Mostafa et al., 2020)
Naproxen	(Diffey et al., 1983, Shelley et al., 1986, Gutiérrez-González et al., 2011, Maerker et al., 2001, Lützow-Holm, 1991, Levy et al., 1990, Rivers and Barnetson, 1989, Farr et al., 1985)
Nebivolol	No cases found
Nefopam	No cases found
Nifedipine	(Cooper and Wojnarowska, 2003, Collins and Ferguson, 1993, Seggev and Lagstein, 1996, Zenarola et al., 1991)
Nitrazepam	No cases found
Nitrofurantoin	(Barratt, 2004)
Nortriptyline	(Bangash et al., 2013)
Olanzapine	(Reddy and Das, 2018, K Singh et al., 2015, Gregoriou et al., 2008)
Omeprazole	(Raison-Peyron et al., 2005)
Oxycodone	No cases found
Pantoprazole	(Correia et al., 2001)
Paracetamol	No cases found
Paroxetine	(Álvarez-Pérez et al., 2012, Rodríguez-Pazos et al., 2011, Vilaplana et al., 2002)
Penicillin	No cases found
Pentoxifylline	No cases found
Phenytoin	(Bhalla et al., 2011)
Pioglitazone	No cases found
Posaconazole	No cases found
Pramipexole	(Tashkent and Aiyappan, 2018)

Drug name	Reference
Pravastatin	(Rodríguez-Pazos et al., 2010, Srivastava et al., 2003)
Prednisolone	No cases found
Pregabalin	(Pérez-Feal et al., 2020)
Prochlorperazine	(Birner and Meyer, 2001, O'Reilly et al., 1999, Rasmussen et al., 1988, Ban and Lehmann, 1965, HAYS et al., 1964)
Promethazine	(Cariou et al., 2020, Arrue et al., 2007, Leong, 1970, Newill, 1960, Epstein and Rowe, 1957)
Propranolol	(Miller and Rampling, 1982)
Quetiapine	No cases found
Quinine sulphate	(Natkunarajah et al., 2010b, Hickey et al., 2007, Nacher et al., 2005, Metayer et al., 2001, O'Reilly et al., 1999, Delmas and Plantin, 1995b, Dawson, 1995, Johnson et al., 1975, Okun et al., 1994, Liunggren et al., 1992, Guzzo and Kaidbey, 1990, Tan et al., 1989, Diffey et al., 1988, Ferguson et al., 1987, Dawson, 1986, Ljunggren and Sjövall, 1986, Thomas and Munro, 1986, Jeanmougin et al., 1984, Calnan, 1978, Wagner et al., 1994, Abreu-Gerke et al., 2000)
Ramipril	(Wagner et al., 2000, Shelley and Shelley, 1992)
Ranitidine	(Kondo et al., 2000, Todd et al., 1995)
Ranolazine	No cases found
Risedronate	No cases found
Rituximab	No cases found
Rivaroxaban	No cases found
Rosuvastatin	(Nardi et al., 2011)
Sacubitril and valsartan (Entresto)	No cases found
Salbutamol	No cases found
Selegiline	No cases found
Senna	No cases found
Seretide	No cases found

Drug name	Reference
Sertraline	(Lin et al., 2009)
Simvastatin	(Korzeniowska et al., 2019, Sommer et al., 2015, Rodríguez-Pazos et al., 2010, Holme et al., 2002, Rodriguez Granados et al., 1998, Morimoto et al., 1995)
Sodium Chloride	No cases found
Solifenacin	No cases found
Somatropin	No cases found
Sotalol	No cases found
Spironolactone	(Schwarze et al., 1998a)
Stalevo	No cases found
Sulfasalazine	(Bouyssou-Gauthier et al., 1999)
Sulindac	(Stern and Bigby, 1984)
Sumatriptan	No cases found
Symbicort (Budesonide & formoterol)	No cases found
Tamoxifen	No cases found
Tamsulosin	(Tan and Yap, 2018)
Teicoplanin	No cases found
Telmisartan	(Viola et al., 2015, Korzeniowska et al., 2019)
Terbinafine	(Bacle et al., 2019, Ramachandran et al., 2017, Kuo and Sivamani, 2014, Spiewak, 2010, Hill et al., 2003, Callen et al., 2001)
Thiamine	No cases found
Thyroxine	No cases found
Timolol	No cases found
Tiotropium	(Perez-Perez et al., 2007)
Tocilizumab	(Hamada et al., 2016)
Topiramate	No cases found
Tramadol	No cases found
Trandolapril	No cases found
Trazodone	(Rongioletti and Rebora, 1986)

Drug name	Reference
Trelegy Ellipta (fluticasone furoate, umeclidinium & vilanterol)	No cases found
Turmeric	No cases found
Ursodeoxycholic acid	No cases found
Valproate	(Hebert and Ralston, 2001)
Venlafaxine	(Vaccaro et al., 2007)
Verapamil	No cases found
Warfarin	No cases found
Zolmitriptan	No cases found
Zopiclone	No cases found

Appendix 6

Published paper from first project

Received: 12 November 2019 | Revised: 19 May 2020 | Accepted: 13 June 2020
DOI: 10.1111/phpp.12583

ORIGINAL ARTICLE

Photodermatology, Photoimmunology & Photomedicine WILEY

Systemic drug photosensitivity—Culprits, impact and investigation in 122 patients

Amirah Alrashidi | Lesley E. Rhodes | Jennifer C. H. Sharif | Firas C. Kreeshan | Mark D. Farrar | Tashmeeta Ahad

Faculty of Biology, Medicine and Health, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Centre for Dermatology Research, Manchester Academic Health Science Centre, University of Manchester and Salford Royal NHS Foundation Trust, Manchester, UK

Correspondence
Lesley Rhodes, Photobiology Unit, Dermatology Centre, University of Manchester, Salford Royal NHS Foundation Trust, Manchester M6 8HD, UK.
Email: Lesley.e.rhodes@manchester.ac.uk

Funding information
Kuwaiti Government and NIHR Manchester Biomedical Research Centre

Abstract

Background: Systemic drugs are a potentially reversible cause of photosensitivity. We explore prevalence, impact, phototest findings and culprit drugs.

Methods: Retrospective review of patients was diagnosed with drug-induced photosensitivity in a specialist photoinvestigation centre (2000-2016), using data recorded in standardized pro forma. Patients underwent detailed clinical evaluation. Monochromator phototesting was performed to 300 ± 5 nm, 320 ± 10 nm, 330 ± 10 nm, 350 ± 20 nm, 370 ± 20 nm, 400 ± 20 nm, 500 ± 20nm and 600 ± 20 nm. Broadband UVA and solar-simulated radiation (SSR) testing were performed, and photopatch testing and laboratory tests examined for other causes of photosensitivity. DLQI was evaluated.

Results: Prevalence of drug-induced photosensitivity was 5.4% (122/2243) patients presenting with photosensitivity. Patients with drug-induced photosensitivity were 52.5% female; median 62 years (range 11-86); phototype I (17.2%), II (39.3%), III (26.2%), IV (6.5%), V (4.1%). Fifty-five (45.1%) patients had reduced erythemal thresholds on monochromator phototesting: 83.6%% to UVA alone, 14.5% to both UVA and UVB, 1.8% to UVA and visible light; 61.4% (n = 75) showed abnormal response to broadband UVR. Drugs implicated: quinine (11.5%), diuretics (10.7%; thiazide 9.8%), antifungals (9.8%), proton-pump-inhibitors (9.8%), angiotensin-converting enzyme inhibitors (7.4%), anti-inflammatory drugs (6.6%), statins (5.7%), selective serotonin reuptake inhibitors (4.9%), calcium channel antagonists (3.3%), anti-epileptics (3.3%), tricyclic antidepressants (3.3%), beta-blockers (2.5%), antibiotics (2.5%), others (≤1.6% cases each). Emerging culprits included azathioprine (2.5%) and biologics (TNF-α inhibitors, denosumab; 2.5%). Median DLQI was 11 (range 2-27) for the past year.

Conclusion: Classically described photosensitizing drugs such as thiazides and quinine remain common offenders, while emerging culprits include biologics such as TNF-a inhibitors and proton-pump-inhibitors. There is very large impact on life quality; identification facilitates measures including drug cessation and implementation of appropriate photoprotection.

Alrashidi and Rhodes are Joint first authors.

KEYWORDS
cutaneous, drug reaction, photodermatoses, prevalence, quality of life

1 | INTRODUCTION

Drug-induced photosensitivity is an important, potentially reversible cause of photosensitivity, and is a potential adverse effect of many medications. While systematic reviews have explored the range of medications causing photosensitivity,[1,2] the prevalence of these drug reactions is largely unknown. A retrospective analysis of reports suggested drug-induced photosensitivity may account for up to 8% of cutaneous adverse effects from drugs.[3] However, estimates of prevalence are likely to be an underestimate as many cases may be undiagnosed or unreported. Studies are largely based on clinical observation, including case series and case reports, with a minority incorporating phototesting.[2] Objective evidence is therefore usually lacking. Moreover, culprit drugs and the expression of drug-induced photosensitivity alter as new drugs emerge. Thus, more awareness is required regarding current culprits, diagnosis and impact on patients.

Mechanisms of drug-induced photosensitivity include phototoxicity, photoallergic reactions and drug-induced lupus erythematosus (LE),[4] with most cases of systemic drug-induced photosensitivity thought to be exerted through phototoxicity. Pathogenesis of phototoxic reactions is secondary to activation of the photosensitizing drug or its metabolite(s) by ultraviolet radiation (UVR) which can then lead to photosensitivity either through direct cellular or oxidative and free radical damage.[4,5] Phototoxicity may theoretically occur in any individual exposed to enough of the drug or relevant wavelength of UVR, although the threshold differs across individuals.[4] Photoallergic reactions to systemic drugs are less common, more often occurring due to topical agents. They are mediated by cell-mediated type IV hypersensitivity responses and require sensitization to the offending drug.[5] With topical though not systemic photoallergy, photopatch testing is usually very useful in determining the causative agents.

Patients with drug-induced photosensitivity can be investigated at a photodiagnostic unit, where their features of photosensitivity are differentiated from those of other photodermatoses. A detailed clinical appraisal is required to explore for culprit drugs, including timing of onset of symptoms and of medication. Clinical features may include burning, itching and a rash affecting sun-exposed sites; this is most often either with a pronounced sunburn-like reaction or with an eczematous rash, while other features including photo-onycholysis, LE and lichenoid reactions occur more rarely. Monochromator phototesting to examine erythemal thresholds to narrowband UVB, UVA and visible radiation helps objectively identify presence of photosensitivity and its action spectrum.[4] Resolution of abnormal responses on retesting or clinical improvement after a several month period of drug cessation can assist confirmation of drug-induced photosensitivity.

Our objectives were to explore the prevalence, impact, current and emerging culprits of drug-induced photosensitivity, in patients with features of photosensitivity investigated at a photodiagnostic unit.

2 | METHODS

2.1 | Patients and methodology

This was a case series of patients diagnosed with drug-induced photosensitivity over a 16-year period (Jan 2000-Jan 2016) in a specialist clinical photoinvestigation centre (Photobiology Unit, Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester, UK). Patients are referred, mainly by general dermatologists, from a wide geographic area of Northern and Central England and Wales, UK. Data were obtained with standardized pro forma and phototest methods. Detailed clinical history was taken from patients with timelines of medications taken and symptoms of photosensitivity and they were examined for signs of a photodistributed rash and its morphology. Detailed monochromator phototesting was performed to narrow bandwidths of UVR and visible radiation from 300 to 600 nm. Additionally, patients underwent broadband phototesting with low-dose UVR on up to 3 consecutive days in accordance with the unit's routine photo-provocation schedule. Photopatch with control patch testing was performed to sunscreen filters and non-steroidal-anti-inflammatory drugs (NSAIDs), along with laboratory tests including connective tissue disease (CTD) screen, urine and blood porphyrin testing and serum 25-hydroxyvitamin-D (25OHD) level. Dermatology Life Quality Index (DLQI) was evaluated, with scores for the past week and the past year.[6]

2.2 | History and examination pro forma

Detailed history and examination were taken using a standardized pro forma to include: age and season at onset; number of episodes per year; whether rash is continuous or present/absent/less severe in winter; any increased tolerance as summer progresses; precipitants of rash; use of sunscreens and whether use helps prevent rash; whether rash can be provoked through window glass; duration of sun exposure needed to provoke rash; duration between exposure to sun and appearance of rash; duration of lesions; symptoms of condition; drug history at the onset of photosensitivity with start and stop dates; present systemic drugs and topical agents with start and stop dates; any significant consumption of food/drink containing psoralens or quinine; previous treatments for the rash including dates; past medical history; family history; phototype; occupation/outdoor activities; effect on quality of life (including restriction in outdoor activity). Examination of rash and available photographs was performed to evaluate morphology and distribution.

2.3 | Photoinvestigation

2.3.1 | Monochromator phototesting

Phototesting against narrow bandwidths of UVB, UVA and visible radiation was performed on the central/upper back to determine the minimal erythemal dose (MED) and define the action spectrum. Patients were exposed to 300, 320, 330, 350, 370, 400, 500 and 600 nm (half-maximum bandwidth 5 nm at 300 nm, 10 nm at 320 and 330 nm; 20 nm at all other wavelengths) using a xenon arc lamp (1 KW short arc, Newport Spectra-Physics Ltd, Didcot, UK) coupled to a 1/4m grating monochromator (Newport Spectra-Physics Ltd) (Table 1). Irradiance was measured using a calibrated thermopile (Medical Physics, Dryburn Hospital, Durham, UK) and digital voltmeter (Medical Physics, Royal Liverpool University Hospital, Liverpool, UK). Patients were exposed on their back to a geometric progression of doses (common ratio = √2) at each wavelength. The lowest dose at which a visible erythemal reaction was induced, that is the MED, was noted at 24 hours.[7]

2.3.2 | Broadband UVR provocation testing

Testing was performed on 5 × 5 cm areas of skin of the ventral forearm. All patients were given 15 J/cm^2 broadband UVA (320-400 nm) using a custom-built arm exposure unit incorporating Cleo Performance™ bulbs (Phillips Healthcare UK Ltd. Guildford UK). Additionally from 2009 onwards, provocation testing was performed on the contralateral forearm using 10J/cm^2 solar-simulated radiation (SSR) (290-400 nm, 1 KW xenon arc plus atmospheric attenuation filter Newport Spectra-Physics Ltd).[7]

2.3.3 | Photopatch testing

This was carried out on the lower back to examine for presence or co-existence of photocontact allergy. From 2009, this involved 24 agents: 19 UV filters, 5 NSAIDs (Chemotechnique Diagnostics, Vellinge, Sweden)[8] and sunscreen products including patients' own, while prior to 2009, the photopatch series comprised 10 agents: 9 organic UV filters and sunscreen products. Duplicate patches were applied (day 1) to skin of the mid-back for 24 hours following which one set was irradiated (day 2) with broadband UVA (5J/cm^2; reduced dose where low erythemal thresholds) (320-400 nm; UVAL 801, Herbert Waldmann GmbH & Co. KG, Villingen-Schwenningen, Germany). Visual readings were taken at 24 and 48 hours post-UVR (days 3, 4) to examine for a response, using the International Contact Dermatitis Research Group (ICDRG) grading.[7,9]

2.4 | Laboratory tests

These included CTD screen, urine and blood porphyrin testing, and serum 25OHD level.

2.5 | Quality of life evaluation

The DLQI is a questionnaire used to assess the quality of life (QoL) which has been validated in dermatology conditions, although not specifically for photosensitivity conditions.[6] The DLQI was completed at the time of photoinvestigation by patients from January 2011 onwards, to assess the impact of drug-induced photosensitivity on QoL both in the past week and past year to take into account seasonal variation.

3 | RESULTS

3.1 | Patient demographics

A total of 2243 patients underwent investigation including phototesting in the photobiology unit from January 2000 to January 2016. Of these, 122 patients were diagnosed with drug-induced photosensitivity, giving a prevalence of 5.4% within this population. Of the 122 patients, 64 were female (52.5%). Median age was 62, with range 11 to 86 years. The

TABLE 1 Monochromator phototesting protocol: wavelengths and doses of UVR and visible radiation used in the determination of erythema thresholds[a]

Wavelength, nm[b]	Dose series (J/cm^2)												
300 (5)	0.0018	0.0025	0.0035	0.005	0.007	0.01	0.014	0.02	0.028	0.04	0.08		
320 (10)	0.13	0.18	0.25	0.35	0.5	0.7	1.0	1.4	2.0	2.5	4.0		
330 (10)	0.31	0.44	0.63	0.90	1.3	1.8	2.5	3.5	5.0	7.0	10	14	
350 (20)	0.63	0.90	1.3	1.8	2.5	3.5	5.0	7.0	10	14	20	25	40
370 (20)	1.8	3.5	7.0	14	20	28	57						
400 (20)	3.5	7.0	14	28	40	57	113						
500 (20)	50												
600 (20)	50												

[a]Extended lower dose ranges are used when thresholds are lower than the doses shown.
[b]Full-width half-maximum bandwidth in parentheses.

frequencies of patients' Fitzpatrick skin types were as follows: I (17.2%), II (39.3%), III (26.2%), IV (6.5%), V (4.1%), VI (0%); not recorded (6.7%).

3.2 | Clinical features

The clinical features presented by patients are shown in relation to their suspected culprit drug (Table 2). The median duration of symptoms was 3 years. While 53.3% of patients reported symptoms occurring mainly in spring-summer months, 37.7% reported symptoms all year round. The majority, 58%, showed features of a phototoxic reaction, that is sunburn-like in appearance. Patients typically reported experiencing a burning erythema with quick onset following sun exposure and accompanying oedema in severe reactions. A substantial minority, 32%, showed predominantly eczematous features, with skin dryness and scaling. Other clinical presentations were occasionally seen, notably including lichenoid reactions relating to quinine and pseudoporphyria with naproxen. A patient taking colesevelam had an immediate wheal and flare response to phototesting, consistent with drug-induced solar urticaria. Some patients with pre-existing polymorphic light eruption (PLE) reported exacerbation of this condition since onset of the culprit drug. A proportion of patients showing acute phototoxicity to voriconazole (n = 11) also showed features of chronic photodamage. This included patients with cheilitis (5/11) and multiple lentigines (2/11). One patient on voriconazole had also developed a squamous cell carcinoma (SCC) on the ear while on voriconazole, with a further SCC 5 years after stopping voriconazole. We refer to our previous review for further information on the clinical characteristics and implications of voriconazole photosensitivity.[10]

3.3 | Phototesting

3.3.1 | Monochromator phototesting

Patient phototesting results are shown in relation to their culprit drug in Table 3. Overall, 45.1% (n = 55) of patients had reduced (abnormal) MED on monochromator phototesting: 83.6% (n = 46) showed reduced MED to monochromator testing with UVA (320-400nm), 14.5% (n = 8) to UVA plus UVB (300-400 nm) and 1.8% (n = 1) to UVA plus visible light (320-500nm). In patients with UVA sensitivity and accompanying UVB and/or visible light sensitivity, MED was reduced to a greater degree in the UVA than UVB or visible light regions. Nineteen (15.6%) of the 122 patients were phototested after the photoactive drug had been discontinued. The frequency of reduced MED seen at each wavelength on monochromator phototesting in patients diagnosed with drug-induced photosensitivity is shown in Figure 1.

3.3.2 | Broadband phototesting

91.8% (n = 112/122) of patients showed a response to broadband UVR; these included 30.3% (n = 37) showing mild erythema only. It is possible that mild erythema can occur on multiple provocation testing even with a UVR dose that is suberythemal when applied once. Therefore, mild erythemal responses were not considered to be pathological. 61.5% (n = 75) of patients had abnormal responses comprising moderate-severe erythema. A minority of patients showed an eczematous clinical appearance (scaling, tiny papules) when reviewed at 24 hours after the 2nd or 3rd provocation. 52.5% (n = 64/122) of patients had abnormal responses to broadband UVA, and 57.0% (n = 53/93) of patients who had SSR provocation performed had abnormal responses. In patients who had both SSR and broadband UVA phototesting performed, 15.1% (n = 14) had abnormal reactions with one source only (SSR only n = 11; broadband UVA only n = 4). Thus, SSR testing was particularly successful, while there was additional benefit from performing both.

3.3.3 | Photopatch testing

Positive photopatch testing to one or more agents with negative control patch testing was seen in 6 of the 122 patients. Agents were ketoprofen 1% (n = 2), butylmethoxydibenzoylmethane/avobenzone (n = 2) and benzophenone-3/oxybenzone (n = 3). In one patient who had a positive photopatch test to benzophenone-3, a relevant previous reaction to sunscreen was reported by the patient and sunscreen photocontact allergy concurrent with the systemic drug photosensitivity was clinically suspected. Additionally, 11 patients showed positive patch testing alone; agents were homosalate, methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M), benzophenone-3, octylmethoxy-cinnamate, benzophenone-4 and patients' own sunscreen products. These findings were unrelated to the patients' systemic drug photosensitivity and patients were advised to avoid products containing these compounds.

3.4 | Laboratory testing

Porphyrin plasma and urine test were positive in 2 of 117 patients. These results were weakly positive urine porphyrin: creatinine ratio in one patient and weakly positive plasma porphyrin peak at 622nm in another patient, which were not considered relevant.

Antinuclear antibody (ANA) tests were positive in 15 of 115 patients. Most (n = 13) had weakly positive ANA titres between 1:20 and 1:100 which were not considered clinically relevant; their clinical features were in keeping with phototoxicity (burning, erythema). The remaining two patients had ANA titres of 1:1000, but again no clinical features suggestive of LE. One showed severe UVA sensitivity to quinine, with phototoxic clinical features; her symptoms and phototest findings resolved on discontinuation of quinine. The remaining patient's reaction was atypical, with clinical features consistent with pseudoporphyria in relation to naproxen treatment of rheumatoid arthritis; histology showed non-specific erosions.

Positive anti-double-stranded DNA (anti-dsDNA; 86 iu/ml; reference range > 10 iu/mL) was found in a patient photosensitive to mesalazine, who had reduced MED to UVA and UVB; clinically, the features fitted better with phototoxicity than drug-induced LE.

TABLE 2 Clinical features of patients presenting with suspected drug photosensitivity

Drug class	Suspected culprit drug	Total n[a]	Sunburn-like n[a]	Eczematous n[a]	Other n[a]
Antimalarials	Quinine	14	2	8	Lichenoid 4
	Hydroxychloroquine	1		1	
Thiazide diuretics	Bendroflumethiazide	10	4	6	
	Hydrochlorothiazide	1	1		
	Indapamide	1	1		
Antifungals	Voriconazole	11	11		Cheilitis 5 Lentigines 2
	Terbinafine	1	1		
Proton-pump inhibitors	Omeprazole[b]	8	4	4	
	Lansoprazole[b]	3	2	1	
	Rabeprazole[b]	1			PLE exacerbated 1
Angiotensin-converting enzyme inhibitors	Lisinopril[b]	2	2		
	Enalapril	3	1	2	
	Ramipril	4	3	1	
Anti-inflammatory	Naproxen	2	1		Pseudoporphyria 1
	Ibuprofen	2	1	1	
	Mefenamic acid	1	1		
	Sulphasalazine	1	1		
	Mesalazine	2	2		
Statins	Simvastatin	5	1	4	
	Atorvastatin	2	1	1	
Selective serotonin reuptake inhibitors	Fluoxetine	4	2	1	Solar urticaria 1
	Sertraline	2	2		
Calcium channel antagonists	Amlodipine	3	1	2	
	Diltiazem	1	1		
Anti-epileptics	Carbamazepine	2	1		LE 1
	Lamotrigine[b]	1		1	
	Phenobarbitone[b]	1	1		
Tricyclic antidepressants	Amitriptyline	2	1		PLE exacerbated 1
	Nortriptyline	2	2		
β-blockers	Bisoprolol[b]	1			PLE exacerbated 1
	Atenolol[b]	2		2	
Antibiotics	Tetracyclines	1	1		
	Ciprofloxacin	1	1		
	Dapsone	1	1		
Immunosuppressants	Azathioprine	3	3		
Biologics	Etanercept[b]	1	1		
	Infliximab[b]	1	1		
	Denosumab[b]	1	1		
Angiotensin-II-receptor antagonists	Candesartan	2	1	1	
Retinoids	Isotretinoin	2	2		
Loop diuretics	Bumetanide	1			PLE exacerbated 1
Antiarrhythmic agents	Amiodarone	1	1		
Antiplatelet agents	Clopidogrel	1	1		

(Continues)

TABLE 2 (Continued)

Drug class	Suspected culprit drug	Total n[a]	Sunburn-like n[a]	Eczematous n[a]	Other n[a]
Other	Allopurinol[b]	1		1	
	Colesevelam[b]	1			Solar urticaria 1
	Gold injection[b]	1		1	
	Levothyroxine[b]	1	1		
	Metformin	1	1		
	Nicorandil[b]	1	1		
	Parthenolide[b]	1	1		
	Tamoxifen[b]	1	1		
	Tamsulosin[b]	1		1	
	Vitamin B12[b]	1	1		
Total		122	71	39	

[a]Number of patients.

[b]Medications not reported to cause drug-induced photosensitivity in a recent review of drug photosensitivity[1] and systematic review of drug phototoxicity.[2] Patients where a further drug may be contributing to the drug photosensitivity; drug listed above/possible contributing drug: infliximab/azathioprine (n = 1), naproxen/bendroflumethiazide (n = 1), ciprofloxacin/ramipril (n = 1), atenolol/diltiazem (n = 1), ibuprofen/quinine (n = 1), amitriptyline/bendroflumethiazide (n = 1), ramipril/diltiazem (n = 1), atorvastatin/omeprazole (n = 1). [Correction added on 14 July 2020, after first online publication: In table 2, 'TASHGold injection' has been corrected to 'Gold Injection' in this version.]

Symptoms resolved on cessation of mesalazine, with normalization of MED. A further patient had positive anti-dsDNA (71 iu/mL), but this was pre-existing in relation to chilblain lupus.

Extractable nuclear antigen (anti-Ro/SSA) was positive in one patient with severe UVA sensitivity, who was felt to have drug-induced LE. Clinical features were severe erythema and oedema affecting sun-exposed sites and were replicated on provocation testing. The patient was taking methyldopa, which is associated with drug-induced LE. However, the onset of symptoms was closely associated with commencement of carbamazepine, which has also been linked to drug-induced LE in case reports, and this was concluded to be the more likely culprit. Anti-La/SSB antibodies were slightly elevated (1.5 U; reference range > 1.0 U) in a patient on voriconazole and considered non-relevant, the patient showing features of a phototoxic reaction.

Serum 25OHD levels were performed in 68 patients: 61.1% had low 25OHD levels: 35.2% (n = 24) were insufficient (25-50 nmol/L) and 25.0% (n = 17) were deficient (<25 nmol/L).

3.5 | Culprit drugs

Suspect drugs are shown (Tables 2 and 3). The drugs comprised both those well known to cause photosensitivity and emerging culprits with little information currently in the literature regarding photosensitivity reactions.

Emerging culprits noted from 2009 onwards, included azathioprine and biologics, that is TNF-α-inhibitors and the anti-RANKL agent, denosumab. Denosumab-induced UVA photosensitivity (350 and 370 nm) was seen in an 86-year-old woman, skin type II, with a background of rheumatoid arthritis. There was one case of etanercept-induced severe photosensitivity to UVA in a 33-year-old woman, skin type II; ANA was mildly positive (1:100 homogenous) but skin biopsy with immunofluorescence did not show evidence of LE. Although on etanercept for several years, cessation of etanercept led to significant clinical improvement of photosensitivity after 6 months with normalization of MED on monochromator phototesting.

A 21-year-old man presented with photosensitivity chronologically linked to infliximab. Although stopping infliximab modestly improved his photosensitivity symptoms, his photosensitivity continued. The patient was taking concomitant azathioprine, and at 8 months following cessation of the azathioprine, there was significant improvement in his photosensitivity, with near normalization of his MED at 300-400nm (UVB + UVA), suggesting possible synergistic effect of azathioprine photosensitivity with infliximab.

Azathioprine-induced photosensitivity was also seen in an 11-year-old girl with skin type II. Monochromator phototesting revealed reduced MED to UVA (320-370 nm) wavelengths. Two further cases of azathioprine-induced photosensitivity were seen: a 25-year-old woman, skin type II, exhibiting UVA sensitivity at 370 nm, and a 53-year-old man, skin type II, with abnormal response to broadband UVA and SSR.

In 8 patients overall, it was possible that a further drug may have been contributing to the drug photosensitivity; culprit drug/potential further culprit: infliximab/azathioprine (n = 1), naproxen/bendroflumethiazide (n = 1), ciprofloxacin/ramipril (n = 1), atenolol/diltiazem (n = 1), ibuprofen/quinine (n = 1), amitriptyline/bendroflumethiazide (n = 1), ramipril/diltiazem (n = 1), atorvastatin/omeprazole (n = 1).

3.6 | Follow-up and repeat phototesting

Once a culprit drug was suspected through detailed history taking and phototesting, patients were advised to stop and substitute this

TABLE 3 Suspected culprit drugs in patients diagnosed with drug-induced photosensitivity and results of phototesting

Drug class	Drug	n	% patients	Broadband phototesting [n abnormal]		Monochromator phototesting [n with reduced MED]		
				UVA[a]	SSR[a]	UVB[a]	UVA[a]	VL[a]
Antimalarials	Quinine	14	12.3%	+ [12]	+ [7]	+ [1]	+ [13]	
	Hydroxychloroquine	1		–	+ [1]	–	–	–
Thiazide diuretics	Bendroflumethiazide	10	9.8%	+ [5]	+ [3]	–	+ [3]	+ [1]
	Hydrochlorothiazide	1		+ [1]	np	–	–	–
	Indapamide	1		(+) [1]	+ [1]	–	–	–
Antifungals	Voriconazole	11	9.8%	+ [2]	+ [5]	–	+ [5]	–
	Terbinafine	1		–	np	–	–	–
Proton-pump inhibitors	Omeprazole	8	9.8%	+ [6]	+ [6]	+ [1]	+ [4]	–
	Lansoprazole	3		+ [1]	+ [1]	–	+ [1]	–
	Rabeprazole	1		+ [1]	(+) [1]	–	–	–
Angiotensin-converting enzyme inhibitors	Lisinopril	2	7.4%	+ [2]	+ [2]	–	–	–
	Enalapril	3		+ [1]	+[1]	–	+[1]	–
	Ramipril[b]	4		+ [3]	+ [1]	–	+ [2]	–
Anti-inflammatory	Naproxen[b]	2	6.6%	+ [1]	+ [1]	–	–	–
	Ibuprofen[b]	2		(+) [1]	(+) [1]	–	–	–
	Mefenamic acid	1		+ [1]	+ [1]	+ [1]	+ [1]	–
	Sulphasalazine	1		+ [1]	np	–	–	–
	Mesalazine	2		+ [2]	+ [1]	+ [1]	+ [1]	–
Statins	Simvastatin	5	5.7%	+ [1]	+ [1]	–	+ [1]	–
	Atorvastatin[b]	2		(+) [2]	+ [1]	–	–	–
Selective serotonin reuptake inhibitors	Fluoxetine	4	4.9%	+ [2]	+ [2]	–	+ [2]	–
	Sertraline	2		+ [1]	+ [1]	–	+ [1]	–
Calcium channel antagonists	Amlodipine	3	3.3%	+ [2]	(+) [2]	+ [1]	+ [2]	–
	Diltiazem	1		–	(+) [1]	–	+ [1]	–
Anti-epileptics	Carbamazepine	2	3.3%	(+) [1]	+ [1]	–	+ [1]	–
	Lamotrigine	1		+ [1]	+ [1]	–	–	–
	Phenobarbitone	1		–	(+) [1]	–	+ [1]	–
Tricyclic antidepressants	Amitriptyline[b]	2	3.3%	–	–	–	–	–
	Nortriptyline	2		–	–	–	–	–

(Continues)

TABLE 3 (Continued)

Drug class	Drug	n	% patients	Broadband phototesting [n abnormal]		Monochromator phototesting [n with reduced MED]		
				UVA[a]	SSR[a]	UVB[a]	UVA[a]	VL[a]
β-Blockers	Bisoprolol	1	2.5%	+ [1]	+ [1]	–	+ [1]	–
	Atenolol[b]	2		+ [2]	np	+[1]	+ [2]	–
Antibiotics	Tetracyclines	1	2.5%	–	–	–	–	–
	Ciprofloxacin[b]	1		+ [1]	+ [1]	–	–	–
	Dapsone	1		+ [1]	+ [1]	–	+ [1]	–
Immunosuppressants	Azathioprine	3	2.5%	+ [2]	+ [2]	–	+ [2]	–
Biologics	Etanercept	1	2.5%	+ [1]	+ [1]	–	+ [1]	–
	Infliximab[b]	1		+ [1]	+ [1]	+ [1]	+ [1]	–
	Denosumab	1		(+) [1]	+ [1]	–	+ [1]	–
Angiotensin-II-receptor antagonists	Candesartan	2	1.6%	(+) [1]	+ [1]	+[1]	+ [1]	–
Retinoids	Isotretinoin	2	1.6%	+ [2]	+ [2]	–	+ [2]	–
Loop diuretics	Bumetanide	1	0.8%	–	–	–	–	–
Antiarrhythmic agents	Amiodarone	1	0.8%	+ [1]	np	–	–	–
Antiplatelet agents	Clopidogrel	1	0.8%	+ [1]	+ [1]	–	–	–
Other	Allopurinol	1	8.2%	+ [1]	+ [1]	–	–	–
	Colesevelam	1		+ [1]	+ [1]	–	+ [1]	–
	Gold injection	1		+ [1]	+ [1]	–	–	–
	Levothyroxine	1		(+) [1]	(+) [1]	–	–	–
	Metformin	1		+ [1]	(+) [1]	–	–	–
	Nicorandil	1		(+) [1]	(+) [1]	–	–	–
	Parthenolide	1		(+) [1]	(+) [1]	–	+ [1]	–
	Tamoxifen	1		(+) [1]	np	–	–	–
	Tamsulosin	1		(+) [1]	(+) [1]	–	–	–
	Vitamin B12	1		+ [1]	–	–	+ [1]	–

[a]np, not performed; + denotes abnormal response on broadband provocation testing/reduced MED on monochromator testing; (+) denotes mild erythema response on broadband provocation testing.

[b]Patients where a further drug may be contributing to the drug photosensitivity; drug listed above/possible contributing drug: infliximab/azathioprine (n = 1), naproxen/bendroflumethiazide (n = 1), ciprofloxacin/ramipril (n = 1), atenolol/diltiazem (n = 1), ibuprofen/quinine (n = 1), amitriptyline/bendroflumethiazide (n = 1), ramipril/diltiazem (n = 1), atorvastatin/omeprazole (n = 1).

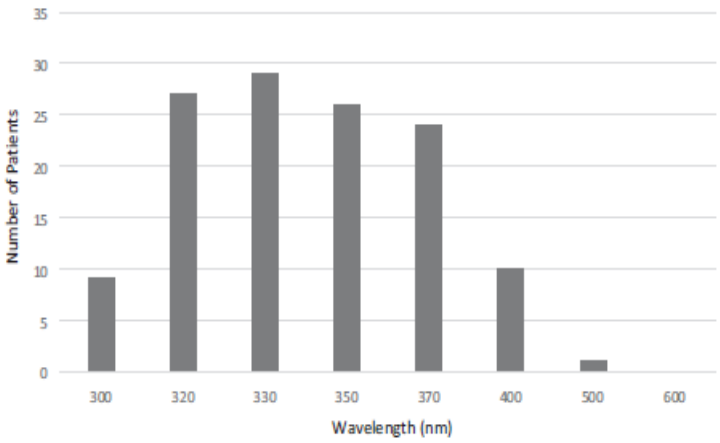


FIGURE 1 Frequency of reduced MED at each wavelength on monochromator phototesting in patients diagnosed with drug-induced photosensitivity

TABLE 4 DLQI scores assessing impact of drug-induced photosensitivity on patient QoL for the past year (n = 58)

No. of patients (%)	DLQI band
1 (2%)	0-1 (no effect)
4 (7%)	2-5 (small effect)
23 (40%)	6-10 (moderate effect)
19 (32%)	11-20 (very large effect)
11 (19%)	21-30 (extremely large effect)

drug if able with guidance of their relevant specialist or general practitioner. In addition, patients were advised on detailed photoprotection measures, including suitable clothing and hats, the use of high UVA protection and sun protection factor (SPF) sunscreens and UVR blocking window films for car, office and home. Vitamin D supplementation of 800 IU daily was recommended in the case of vitamin D deficiency or insufficiency.

Sixty patients re-attended the photobiology unit, the majority reporting complete resolution of symptoms after cessation of the culprit drug, while 14 reported persistent symptoms. Of the latter, 3 patients were unable to stop the suspect drugs (omeprazole, ciprofloxacin/ramipril, lansoprazole) for medical reasons. A further patient (on bendroflumethiazide), was diagnosed to have photoaggravated eczema. Of the remaining ten patients, photosensitivity resolution was clinically incomplete (suspect drugs: simvastatin n = 2, lansoprazole n = 1, omeprazole n = 1, quinine n = 2, indapamide n = 1, candesartan n = 1, fluoxetine n = 1, sulphasalazine n = 1); those taking additional photoactive drugs were then advised to visit their regular physician to discuss potential cessation/ substitution of these.

Repeat phototesting was performed in 26 of the 60 patients. This confirmed resolution of photosensitivity in 18 patients following cessation of the suspect drug (bumetanide n = 1, bendroflumethiazide n = 1, quinine n = 5, lisinopril n = 1, allopurinol n = 1, atenolol n = 1, etanercept n = 1, naproxen n = 1, isotretinoin n = 1, mesalazine n = 1, sertraline n = 1, omeprazole n = 1, colesevelam n = 1, infliximab n = 1). Incomplete or lack of resolution of abnormal phototest results was seen in 7 patients following drug cessation (simvastatin n = 1, lansoprazole n = 1, omeprazole n = 1, quinine n = 2, fluoxetine n = 1, sulphasalazine n = 1). Additionally, phototesting remained abnormal in the patient taking ciprofloxacin/ramipril who was unable to stop these drugs.

3.7 | Dermatology life quality index

The DLQI questionnaire, introduced routinely in 2011, was completed by 58 patients at the time of photoinvestigation (Table 4). A higher impact was seen for the past year than the past week, with many patients visiting the photoinvestigation unit in winter time. Median DLQI score was 6 (range 0-29) for the past week and 11 (range 2-27) for the past year.

4 | DISCUSSION

Drug-induced photosensitivity is an important potentially reversible cause of photosensitivity, with 5.4% of patients undergoing photoinvestigation in our unit between 2000 and 2016 showing photosensitivity attributable to this. Within other specialist photoinvestigation units, drug-induced photosensitivity has been reported to account for between 2% and 15% of photodermatoses diagnosed, including 4% in the Scottish Photobiology service.[4,11-15] It is likely that this is the tip of the iceberg, as many drugs have the potential to photosensitize, whereas only selected patients will achieve referral to scarce tertiary diagnostic units.

Our review shows that the previously reported common photosensitizing drugs remain top of the list, in particular quinine and thiazide diuretics, responsible for 11.5% and 9.8% of cases of drug-induced photosensitivity, respectively. A high percentage of patients with voriconazole-induced photosensitivity (9%) was observed, attributable to our close geographic links with the UK National Aspergillosis Centre, while reactions to proton-pump inhibitors (PPI) were also prevalent (9.8%).

Overall, findings are comparable to those of other photoinvestigation centres, such as the Scottish Photobiology service, where commonly found culprits of drug-induced photosensitivity included thiazide diuretics, amiodarone, NSAIDs, quinine, doxycycline and calcium channel antagonists.[4] Commonly reported culprits of systemic drug-induced photosensitivity in the literature include diuretics, specific antibiotics, antifungals, antipsychotics, calcium channel antagonists, amiodarone, retinoids, quinine and NSAID, which remained culprits in our review.[4,5,16-23] However, our analysis also reveals higher frequencies of drug-induced photosensitivity associated with PPI, angiotensin-converting enzyme inhibitors and statins, which were not among the previously reported common culprits, potentially reflecting an increase in prescription of these drugs. A recent review listed 2 reports of suspected drug-induced photosensitivity reactions to the PPI pantoprazole and esomeprazole.[1] Our findings also suggest occasional reactions to drugs that were not included as culprits in a recent review of drug-induced photosensitivity[1] and a systematic review of drug phototoxicity,[2] including the beta-blockers bisoprolol and atenolol (while tilisolol was reported[1]), lamotrigine, phenobarbitone, levothyroxine, allopurinol, colesevelam, parthenolide, tamoxifen, tamsulosin, vitamin B12, nicorandil and gold injection.

Our report has revealed further emerging culprits with previously limited reports in the literature. Sometimes involving younger patients (age < 35), these culprits included azathioprine and biologics, that is TNF-α inhibitors and denosumab. Severe UVA photosensitivity to azathioprine was seen in 3 patients (also in a 4th patient treated with infliximab and azathioprine), contrasting with the more modest skin photosensitivity to UVA previously reported on azathioprine.[24,25] Perrett et al demonstrated reduced MED to UVA and SSR in a series of 5 patients taking azathioprine, with no abnormal response to UVB.[24] Of concern, azathioprine is also associated with photocarcinogenesis; this is thought to be exerted through metabolites such as 6-thioguanine causing promutagenic oxidative DNA damage following interaction with UVA.[24,25]

Our series also revealed one case of etanercept-induced photosensitivity to UVA, and a further case of possible potentiation of UVA and UVB photosensitivity to azathioprine by infliximab. TNF-α inhibitors have been associated with a variety of cutaneous reactions, including psoriasis, sebopsoriasis, pustulosis, eczematous, bullous, granulomatous, lichenoid and vasculitic rashes,[26] and have also been widely associated with drug-induced LE,[27,28] which may contribute to photosensitivity. However, no similar reports of severe photosensitivity as seen in our cases have, as far as we are aware, been reported.

We found one case of photosensitivity related to denosumab, an anti-RANKL biologic administered subcutaneously to treat osteoporosis. Although there is scarce mention of denosumab-induced photosensitivity in the literature, FDA reports have linked denosumab to photosensitivity; this was seen in 6 treated patients versus 1 on placebo in a phase III randomized clinical trial involving 7800 postmenopausal women with osteoporosis.[29]

In recent years, cases of photosensitivity have been reported with newer drugs including cancer therapies such as BRAF kinase inhibitors, for example vemurafenib and dabrafenib, epidermal growth factor receptor (EGFR) inhibitors and other anticancer therapies.[4] No cases were seen in our photoinvestigation centre in relation to these agents, perhaps due to awareness and management of the cutaneous adverse effects by the oncology community.

What makes certain patients more likely to develop drug-induced photosensitivity is unclear. It is probable that genetic factors, such as polymorphisms in genes encoding drug-metabolizing enzymes, antioxidant properties and sensitivity to UVR play a role.[4] We found the gender balance of patients to be equal (female 52.5%, n = 64). The median age was 62 years, reflecting that older patients are more likely to be on medications, especially multiple medications, thus increasing their risk of drug-induced photosensitivity.

Drug-induced photosensitivity had a very large or extremely large impact on patients' QoL in half of patients completing the questionnaire, with a median DLQI of 11 for the past year for all patients. This was comparable to other photodermatoses, where median DLQI scores of greater than 10 for the past year were seen, for example, in actinic prurigo and photoaggravated dermatoses in a multicentre assessment of 790 patients with photodermatoses.[30] QoL in drug-induced photodermatosis was also assessed in a cohort of 26 patients in that multicentre study, although this was conducted by postal questionnaire at a time point subsequent to patient diagnosis. It was found that 23% of patients scored a DLQI of >10, compared to 51% of 58 patients who completed the DLQI questionnaire at the time of photoinvestigation in our patients.

In our series, phototesting via monochromated and broadband UVR provides an objective method of confirming photosensitivity, alongside a typical clinical history and evaluation for drug photosensitivity. Nearly half, that is 45.1% patients, had reduced MED on monochromator phototesting. Some patients had already stopped taking the culprit drug before attending the photodiagnostic unit, potentially explaining their normal MED on monochromator phototesting. Interestingly, the yield of abnormal responses was increased by the addition of broadband phototesting; this might be anticipated in view of the broad action spectrum demonstrated by several phototoxic drugs.[4] The majority of lowered MED were to UVA alone, and while a number occurred to UVB in addition to UVA, none were seen to UVB alone (Table 3). Only one patient, taking bendroflumethiazide, showed lowered MED to UVA plus visible light. This action spectrum was anticipated, that is reflecting the frequency of UVA > UVB > visible light activation.[4]

Limitations of this study include the challenges in identifying culprit drugs in patients who take several medications and where a concurrent photodermatosis, such as photoaggravated eczema, may confound presentation. There is no definitive diagnostic test for drug photosensitivity, and consequently, this diagnosis is inevitably largely presumed rather than proven. It would be optimal for photodiagnostic units to follow up all patients suspected of drug photosensitivity, including repeat phototesting, although this is often not practically possible. All our patients are offered follow-up appointments, but as many travel long-distance to the specialist unit, they often arrange to return only if their symptoms persist, deferring their appointment if they resolve.

In conclusion, we find drug-induced photosensitivity occurred in 5.4% patients referred to a specialist photoinvestigation unit and suspect a much larger population of patients fails to be suspected and referred. Classical photosensitizing drugs such as quinine and thiazides remain common culprits; physicians should be aware of these as well as emerging culprits including the biologics, PPI and statins. Drug-induced photosensitivity causes very high impact on QoL and is vital to suspect in view of its potentially curable nature. Early suspicion, identification, consideration of phototesting/repeat phototesting alongside cessation of culprit drugs where feasible, and implementation of photoprotection, are key measures.

ACKNOWLEDGEMENTS

The study was funded by the Kuwaiti Government and the National Institute of Health Research Manchester Biomedical Research Centre.

CONFLICT OF INTEREST

None declared.

ORCID

Lesley E. Rhodes https://orcid.org/0000-0002-9107-6654
Mark D. Farrar https://orcid.org/0000-0001-8602-7279
Tashmeeta Ahad https://orcid.org/0000-0002-0061-6011

REFERENCES

1. Blakely KM, Drucker AM, Rosen CF. Drug-induced photosensitivity—an update: culprit drugs, prevention and management. *Drug Saf*. 2019;42:827-847.
2. Kim WB, Shelley AJ, Novice K, Joo J, Lim HW, Glassman SJ. Drug-induced phototoxicity: a systematic review. *J Am Acad Dermatol*. 2018;79:1069-1075.
3. Selvaag E. Clinical drug photosensitivity. A retrospective analysis of reports to the Norwegian Adverse Drug Reactions Committee from the years 1970–1994. *Photodermatol Photoimmunol Photomed*. 1997;13:21-23.
4. Ibbotson S. Drug and chemical induced photosensitivity from a clinical perspective. *Photochem Photobiol Sci*. 2018;17:1885-1903.
5. Mang R, Stege H, Krutmann J. Mechanisms of phototoxic and photoallergic reactions. In: Johansen JD, Frosch PJ, Lepoittevin JP, eds. *Contact Dermatitis*., Berlin, Heidelberg: Springer; 2011:155-163.
6. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210-216.
7. Haylett AK, Koumaki D, Rhodes LE. Solar urticaria in 145 patients: Assessment of action spectra and impact on quality of life in adults and children. *Photodermatol Photoimmunol Photomed*. 2018;34:262-268.
8. Kerr AC, Ferguson J, Haylett AK, et al. A European Multicentre Photopatch Test Study (EMCPPTS). *Br J Dermatol*. 2012;166:1002-1009.
9. Wilkinson DS. Terminology of contact dermatitis. *Acta Derm Venereol*. 1970;50:287-292.
10. Haylett AK, Felton S, Denning DW, Rhodes LE. Voriconazole-induced photosensitivity: photobiological assessment of a case series of 12 patients. *Br J Dermatol*. 2013;168:179-185.
11. Kerr HA, Lim HW. Photodermatoses in African Americans: a retrospective analysis of 135 patients over a 7-year period. *J Am Acad Dermatol*. 2007;57:638-643.
12. Khoo SW, Tay YK, Tham SN. Photodermatoses in a Singapore skin referral centre. *Clin Exp Dermatol*. 1996;21:263-268.
13. Stratigos AJ, Antoniou C, Papathanakou E, et al. Spectrum of idiopathic photodermatoses in a Mediterranean country. *Int J Dermatol*. 2003;42:449-454.
14. Wadhwani AR, Sharma VK, Ramam M, Khaitan BK. A clinical study of the spectrum of photodermatoses in dark-skinned populations. *Clin Exp Dermatol*. 2013;38:823-829.
15. Wong SN, Khoo LS. Analysis of photodermatoses seen in a predominantly Asian population at a photodermatology clinic in Singapore. *Photodermatol Photoimmunol Photomed*. 2005;21:40-44.
16. Ferguson J. Photosensitivity due to drugs. *Photodermatol Photoimmunol Photomed*. 2002;18:262-269.
17. Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol*. 1995;33:551-573.
18. Zuba EB, Koronowska S, Osmola-Mankowska A, Jenerowicz D. Drug-induced Photosensitivity. *Acta Dermatovenerol Croat*. 2016;24:55-64.
19. Drucker AM, Rosen CF. Drug-induced photosensitivity culprit drugs. *Drug Saf*. 2011;34:821-837.
20. Monteiro AR, Rato M, Martins C. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. *Clin Dermatol*. 2016;34:571-581.
21. Dawe RS, Ibbotson SH. Drug-induced photosensitivity. *Dermatol Clin*. 2014;32:363-368.
22. Ibbotson SH. Shedding light on drug photosensitivity reactions. *Br J Dermatol*. 2017;176:850-851.
23. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Saf*. 2002;25:345-372.
24. O'Donovan P, Perrett CM, Zhang X, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. *Science*. 2005;309:1871-1874.
25. Perrett CM, Walker SL, O'Donovan P, et al. Azathioprine treatment photosensitizes human skin to ultraviolet A radiation. *Br J Dermatol*. 2008;159:198-204.
26. Moran GW, Lim AW, Bailey JL, et al. Review article: dermatological complications of immunosuppressive and anti-TNF therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;38:1002-1024.
27. Ramos-Casals M, Brito-Zerón P, Soto MJ, Cuadrado MJ, Khamashta MA. Autoimmune diseases induced by TNF-targeted therapies. *Best Pract Res Clin Rheumatol*. 2008;22:847-861.
28. Wetter DA, Davis MD. Lupus-Like Syndrome Attributable to Anti–Tumor Necrosis Factor α Therapy in 14 Patients during an 8-Year Period at Mayo Clinic. *Mayo Clin Proc*. 2009;84:979-984.
29. Rothstein A. Denosumab Safety: FDA Analysis. Silverspring, MD: FDA; (nd.) Available from: https://courses.washington.edu/bonephys/denosumab/FDA%20denosumab%20background.pdf. Accessed June 29, 2020.
30. Jong CT, Finlay AY, Pearse AD, et al. The quality of life of 790 patients with photodermatoses. *Br J Dermatol*. 2008;159:192-197.

How to cite this article: Alrashidi A, Rhodes LE, Sharif JCH, Kreeshan FC, Farrar MD, Ahad T. Systemic drug photosensitivity—Culprits, impact and investigation in 122 patients. *Photodermatol Photoimmunol Photomed*. 2020;00:1–11. https://doi.org/10.1111/phpp.12583

l