

Drug-induced Photosensitivity: Clinical and Etiological Study in Tunisia

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Abstract

Background: Photosensitization is a cutaneous reaction that occurs following exposure to sunlight. It may present as phototoxicity or as photoallergy, an immunologically mediated reaction.

The aim of this study was to describe the epidemiological and clinical characteristics of patients with drug-induced photosensitivity in Tunisia and to identify the implicated medications.

Methods: We conducted a retrospective study over an 11-year period, including all cases of drug-induced photosensitivity reported to the National Pharmacovigilance Center (CNPV).

Results: A total of 130 cases were analyzed. The median age was 58 years (range: 8–83), with a female-to-male ratio of 1.95. Time to onset of symptoms after drug intake ranged from 6

hours to 20 years, with a median of 60 days. Phototoxic reactions represented 81.5 % of cases, most commonly presenting as erythema (84.9 %). Photoallergic reactions predominantly manifested as eczema, localized to photo-exposed areas in 18 cases and extending to covered regions such as the trunk and back in 6 cases. Clinical improvement following drug withdrawal was observed in 61.5 % of patients. The most frequently implicated drug classes were cardiovascular medications (46.7 %) and anti-infectives (16.9 %).

Conclusion: Although relatively uncommon, drug-induced photosensitivity should be promptly recognized by clinicians, as it can result in cosmetic and medical complications. Early discontinuation of the causative drug usually ensures resolution, while strict photoprotection remains essential to prevent recurrences. Importantly, chronic or repeated photosensitization may increase the long-term risk of photocarcinogenesis, underscoring the need for vigilance during high-risk treatments.

Keywords: drug-induced photosensitivity; phototoxicity; photoallergy; pharmacovigilance; adverse drug reaction

INTRODUCTION

Photosensitization is a cutaneous reaction that occurs following exposure to sunlight [1]. It results from the interaction between a photosensitizing substance (chromophore) and an effective wavelength. Drug-induced photosensitivity arises from the combination of drug administration and sun exposure [2]. It is classified into two categories according to the underlying pathophysiological mechanism: phototoxicity and photoallergy [3].

Phototoxicity is more common and results from a photochemical reaction that directly damages cells. Photoallergy, in contrast, is a cell-mediated immune response. The distinction between these two entities is based on clinical history, physical examination, histological findings, and photobiological testing. However, differentiation may sometimes be challenging [4].

Drug-induced photosensitivity can lead to cosmetic concerns and, in severe cases (e.g., bullous lesions), may increase the risk of secondary infections. In addition, chronic or recurrent photosensitivity has been associated with the development of skin cancers [4, 5].

This adverse drug reaction (ADR) occurs more frequently in fair-skinned populations or in regions with high sun exposure, such as Tunisia^[3]. Given the scarcity of data on drug-induced photosensitivity in Tunisia, we conducted this study to describe its epidemiological and clinical characteristics and to identify the drugs implicated, based on cases reported to the National Pharmacovigilance Center (CNPV).

METHODS

We conducted a retrospective descriptive study over an 11-year period, from January 2012 to December 2023. All reported cases of patients who developed photosensitivity, erythema, or eczema localized to sun-exposed areas following drug intake, and notified to the Department of Pharmacovigilance in the Tunisian National Centre of Pharmacovigilance were included. Patients referred to the department who did not present with photosensitivity, erythema, or eczema were not included. We also excluded cases in which erythema or eczema was not attributed to photosensitivity, or when the drug's responsibility could not be established.

Drug imputability was assessed according to the updated French method of causality assessment^[6]. This approach considers both intrinsic and extrinsic imputability. Intrinsic imputability is determined using chronological criteria (time to onset relative to drug administration, evolution after withdrawal or continuation, and response to re-exposure) and semiological criteria (clinical or biological features suggestive of drug involvement). Extrinsic imputability is based on published literature, evaluating whether the adverse reaction is already known or represents a new finding.

RESULTS

The study included 130 cases of drug-induced photosensitivity, representing 0.37% of all adverse event reports received by the CNPV during the study period.

Among cases of photosensitivity, 33.8% occurred in winter and 28.5% in spring. Dermatologists were the reporting physicians in 50.7% of cases.

Patients' ages ranged from 8 to 83 years (median: 58 years). There were 86 women (66.1%) and 44 men (33.9%), with a female-to-male ratio of 1.95.

Based on the underlying mechanism, cases were classified as phototoxicity (106 cases, 81.5%) or photoallergy (24 cases, 18.5%).

1. Cases of phototoxicity

Among the 106 patients who developed phototoxicity, the main clinical features were erythema (84.9%), hyperpigmentation (14.2%) and one case of isolated photo-onycholysis (0.9%). Phototoxicity was associated with pruritus in 40.6% of cases.

Lesions were confined to sun-exposed areas, primarily affecting the face (99% of cases) and the hands and forearms (73.8%) (Figure 1).

The latency between drug initiation and onset of phototoxicity ranged from 6 hours to 20 years, with a mean of 60 days.

Resolution of symptoms occurred in patients who discontinued the culprit drug, with a mean duration of 9 days (range: 1-120 days). In patients who did not discontinue the drug immediately, 9 cases resolved under photo-protection, while in the others, lesions persisted without progression during follow-up of up to 3 months.

Drug associated with phototoxicity:

All suspected drugs were administered orally. In 84 cases, a single drug was implicated, whereas in 22 cases, two or more drugs were suspected.

Cardiovascular drugs were the most frequently involved, reported in 59 cases (43.4%), including antihypertensives in 43 cases (31.7%) and hypolipidemic agents in 12 cases. Anti-infective agents were implicated in 25 cases (18.4%), while antineoplastics and immunomodulators were involved in 18 cases (13.3%). Non-steroidal anti-inflammatory drugs (NSAIDs) and antimalarials were each implicated in 6 cases, followed by antiepileptics in 5 cases. Phenothiazines accounted for 3 cases, and a single case of phototoxicity was observed with isotretinoin. Overall, 63 active substances were identified (Table 1). The most frequently implicated drugs were captopril (10 cases), hydrochlorothiazide (8 cases), and atorvastatin (6 cases). Other commonly involved agents, each responsible for 5 cases, were amlodipine, doxycycline, fenofibrate, paclitaxel and irbesartan.

Using the French method of causality assessment, scores were I1 (doubtful) in 103 cases and I3 (likely) in only 3 cases. In the three likely cases, a positive rechallenge was documented with carbamazepine, ciprofloxacin and spironolactone. No cases of severe phototoxicity were reported.

2. Cases of photoallergy

Among the 24 patients who developed photoallergy, eczematiform lesions were noted in 16 cases (Figure 2), urticarial lesions in 7 cases, and lichenoid eruption in 1 case. Pruritus accompanied the eruption in 16 patients.

In 6 patients, skin lesions were also present on non-sun-exposed sites, including the chest and back.

The latency between drug initiation and onset of photoallergic reactions ranged from 1 day to 5 years, with a mean of 45 days.

Resolution of symptoms occurred in all 15 cases in which the culprit drug was withdrawn. In the remaining 9 cases, lesions persisted without progression during follow-up of up to 6 months.

Drug related to photoallergy:

All suspected drugs were administered orally. Among the 24 patients, a single drug was taken in 21 cases, while two or more drugs were implicated in 3 cases.

Cardiovascular drugs were involved in 18 cases, including antihypertensives in 10 cases and hypolipidemic agents in 8 cases. Anti-infective drugs were implicated in 3 cases and NSAIDs in 3 cases. Overall, 17 active ingredients were identified (Table 2). The most frequently implicated drugs were fenofibrate (5 cases), captopril (4 cases), and atorvastatin (3 cases) and hydrochlorothiazide (3 cases).

According to the French method of causality assessment, all cases were scored as II (doubtful).

3. Comparison between cases of phototoxicity and photoallergy

We analyzed the relationship between therapeutic drug classes and the mechanism of drug-induced photosensitivity. No statistically significant differences were observed in the occurrence of phototoxicity versus photoallergy for the following comparisons: antihypertensives versus other drug classes, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists versus other antihypertensives or antibacterials, antineoplastics, and NSAIDs versus other drug classes.

A statistically significant difference was observed for lipid-lowering agents compared to other drug classes ($p < 0.05$), with phototoxic reactions occurring more frequently than photoallergic reactions.

DISCUSSION

Drug-induced photosensitivity is an uncommon ADR, affecting approximately 1-10% of patients [7-8] and accounting for about 8% of all toxidermias [9]. Its prevalence varies depending on the photosensitizing drug and individual susceptibility [9]. In our study, drug-induced photosensitivity represented only 0.37% of all adverse events reported to the CNPV during the study period. This low prevalence may be attributed to several factors: patients often do not seek medical attention when symptoms resolve after drug withdrawal; diagnosis can be challenging due to overlapping features with sunburn or other dermatological conditions; and under-reporting is common given the generally mild nature of this ADR [3, 10]. Collectively, these factors contribute to an underestimation of its true incidence.

All patients in our series were referred by physicians, with dermatologists reporting half of the cases, reflecting the exclusively cutaneous manifestation of these reactions. The most commonly affected age group was adults, consistent with the findings of Kahri where adults represented 70% of cases and fewer than 10 cases occurred in children [11]. Pediatric data remain limited due to the rarity of drug-induced photosensitivity in children. Similar to prior studies, women were more frequently affected than men, with a female-to-male ratio of 1.95 [12-14], likely because the cosmetic impact of photosensitivity prompts women to seek medical advice more often. Seasonal distribution in our cohort showed that 33.8% of cases occurred in winter and 28.5% in spring, contrasting with previous reports of higher incidence in late summer and early autumn, when sun exposure is maximal [15]. This pattern may reflect high levels of sunlight in Tunisia, leading patients to adopt photoprotection measures in summer while relaxing these precautions in winter. Additionally, unlike ultraviolet B (UVB) rays, which vary seasonally, ultraviolet A (UVA) rays remain constant throughout the year [11]. Drug-induced photosensitivity is predominantly triggered by UVA. UVA represents the majority of solar radiation reaching the earth's surface, penetrates more deeply into the dermis due to its longer wavelength, and interacts with cutaneous chromophores to initiate photochemical and immune response [9].

Drug-induced photosensitivity is typically classified into two types: phototoxicity and photoallergy, which differ in their underlying mechanisms. In our study, cases were categorized accordingly based on clinical features. Phototoxicity was the most frequent type which aligns with previous reports [3, 13, 16].

Phototoxicity is a photochemical reaction that can occur upon first sun exposure, with severity depending on both UV dose and drug concentration. Clinically, it presents as sunburn-like erythema localized to photo-exposed areas, often accompanied by pruritus and a burning sensation [3]. In some cases, it may also result in delayed hyperpigmentation, resembling phytophotodermatitis [5, 17]. Importantly, phototoxicity affects all skin types, although individuals with lighter skin are more susceptible, as even a low dose of UV radiation can trigger pronounced reactions [18]. In our cohort, phototoxic reactions were confined to photo-exposed areas, with a sharp demarcation between affected and unaffected skin [3, 9]. Histologically, phototoxicity is characterized by keratinocyte necrosis with dermal lymphocyte and neutrophil infiltrates. Commonly affected sites included the face, forearms, dorsal hands, anterior legs, nape of the neck, and the V area of the chest [19]. Symptoms typically appear within 30 minutes to 24 hours after sun exposure [3], although delayed reactions occurring several months or even years have also been reported [2, 4]. These cases suggest that, although the association is more difficult to establish with very long latency, delayed phototoxicity remains possible. The clinical course in our patients was comparable to published data, with resolution of symptoms usually within 8-10 days after discontinuation of the drug, although as highlighted in the literature, complete resolution in some cases may require months [9, 20].

Photoallergy, on the other hand, is an immune-mediated photosensitivity reaction. It develops when UV radiation alters the structure of a photosensitizing drug, converting it into a photoantigen capable of eliciting a type IV cell-mediated hypersensitivity response. Unlike phototoxicity, photoallergy requires prior sensitization and is independent of drug concentration or UV dose. Clinically, it typically manifests as a pruritic eczematous eruption [3, 9], although urticaria or lichenoid forms have been reported [19]. A distinctive feature is that, while lesions primarily occur on sun-exposed areas, they may also extend to non-exposed sites, reflecting the immunological mechanism. Histology shows epidermal spongiosis, vesiculation, lymphocyte exocytosis, and perivascular inflammation [19-22]. Symptoms generally appear at least 24 hours after sun exposure [8]. As in other delayed-type

hypersensitivity reactions, the initial sensitization period usually requires 5-15 days, but upon re-exposure to the same hapten, symptoms may reappear within 24 hours or less [14]. Lesions generally improve after discontinuation of the culprit drug and treatment with topical corticosteroids and antihistamines [5]. However, compared with phototoxicity—which usually resolves within 8 to 10 days—the resolution of photoallergy is slower, and in some cases it may persist or evolve into a chronic form [19]. In our series, photoallergic reactions were primarily eczematous, with occasional involvement of non-photo-exposed areas.

Drug-induced photosensitivity is an important consideration in phototherapy clinics and is routinely assessed during patient evaluation. However, published lists of photosensitizing drugs are often incomplete or inaccurate, limiting their usefulness as a reliable reference for clinical practice. A recent review by Hofmann et al. identified 393 agents associated with photosensitivity, predominantly nervous system drugs (20.3%), anti-infectives (17.8%), cardiovascular agents (15.2%), NSAIDs (9.6%), and antineoplastic agents (11.9%) [3]. In contrast, a review by korzeniowska et al. found that cardiovascular drugs and NSAIDs were the most frequent culprits [23].

In our study, 68 active substances were implicated in 130 cases of drug-induced photosensitivity. Cardiovascular agents represented nearly half of all cases (46.7%), followed by anti-infectives (16.9%), and antineoplastic/immunomodulating agents (10.8%). Drugs acting on the nervous system, antimalarials, musculoskeletal agents, and those affecting the digestive system/metabolism each contributed 4%-7%. Among cardiovascular agents, anti-hypertensives predominated (32.1 %) with angiotensin converter enzyme (ACE) inhibitors (mainly captopril) most frequently implicated (13.3%), consistent with previous reports [23, 24]. Angiotensin II receptor blockers (ARBs) were less common, with irbesartan the most frequent [23, 25]. Thiazide diuretics, mainly hydrochlorothiazide, accounted for 9.1% of cases. Hydrochlorothiazide has been recognized as a photosensitizer since the mid-20th century, with the incidence of thiazide-associated photosensitivity estimated at 1-100 cases per 100,000 treated patients [9, 23, 26].

Lipid-lowering drugs also contributed a significant proportion of cases. Statins, although widely prescribed, are rarely implicated; simvastatin has been linked more often to photoallergy, while data on atorvastatin are limited [27]. In our series, 20 cases were attributed to lipid-lowering drugs, with atorvastatin implicated in nine cases, rosuvastatin in

one, and fenofibrate in ten. Fenofibrate was equally split between phototoxicity and photoallergy. A statistically significant difference in the mechanism of photosensitivity was observed between lipid-lowering drugs and other classes, likely reflecting the high photoallergic potential of fenofibrate [27, 28].

Antiarrhythmic drugs, notably amiodarone, were associated with three phototoxic cases. Amiodarone is well known to induce photosensitivity due to its haloaromatic chemical structure, which is particularly sensitive to UV radiation [29]. Reported incidence rates of amiodarone-induced phototoxicity range from 25% to 75% of treated patients [26].

Anti-infective agents formed another major group of photosensitizers. Tetracyclines, particularly doxycycline, are frequently associated with photosensitivity in the literature, owing to their broad UVA absorption spectrum. Reported incidence rates of tetracycline-induced photosensitivity vary widely, ranging from 4 % to 42 % across different series [26, 30]. In our cohort, tetracyclines were implicated in five cases of phototoxicity (3 %), all related to doxycycline. Similarly, quinolone antibiotics have been recognized as photosensitizers, with an estimated incidence of 1-3% of treated patients [26, 30-32]. In our study, only three cases of fluoroquinolone-induced photosensitivity were identified.

Among antifungals, voriconazole is particularly phototoxic, and prolonged use has been associated with squamous cell carcinoma, even in children [7]. Its phototoxicity is thought to arise from either inhibition of retinoid metabolism, leading to elevated vitamin A levels, or from its main metabolite, voriconazole N-oxide, which efficiently absorbs UV radiation [26]. In our series, six cases of photosensitivity were associated with antifungal agents. Azoles accounted for four of these cases, including fluconazole (n=3) and voriconazole (n=1).

Antineoplastic agents were also well-established triggers, and in our series, all associated cases were phototoxic. This is consistent with the literature, which describes chemotherapy, targeted therapies, and immune checkpoint inhibitors as predominantly phototoxic [26, 33]. Targeted therapies are emerging contributors; among them, vemurafenib, a BRAF inhibitor used for advanced melanoma, is particularly notable, with photosensitivity reported in 35–63% of patients in a recent review of its cutaneous adverse effects [34].

NSAIDs, especially propionic acid derivatives such as ketoprofen, tiaprofenic acid, and naproxen, are a heterogeneous group with recognized photosensitizing potential. In our series, nine cases were attributed to NSAIDs, most frequently ketoprofen [23, 26].

Among antimalarials, hydroxychloroquine and chloroquine are generally considered photoprotective, but rare cases of photosensitivity confirmed by photopatch tests have been reported [35-37]. In our series, eight cases of phototoxicity were observed, predominantly associated with hydroxychloroquine.

One case of phototoxicity was associated with isotretinoin in our series. Literature data are conflicting; while some studies suggest skin fragility, phototesting results are inconsistent, and evidence for true photosensitivity remains inconclusive [4, 38].

Taken together, these findings illustrate that, while a wide range of drug classes may induce photosensitivity, certain agents—such as captopril, hydrochlorothiazide, doxycycline, antineoplastic therapies and ketoprofen—consistently emerge as recurrent culprits across studies.

All reactions in our series followed oral drug intake, and no cases of topical photosensitivity were reported. However, topical drug phototoxicity and photoallergy remain an important area of study. Because topical formulations are directly exposed on the skin surface, photolabile compounds are more vulnerable to sunlight-induced degradation [39-41]. Clinically, topical photosensitivity is often easier to recognize than systemic reactions, as lesions are confined to photo-exposed sites in contact with the photosensitizer. Photopatch testing is pivotal for identifying the responsible photoallergen in these cases [19]. Although topical phototoxic and photoallergic reactions are relatively common in dermatology practice, large-scale clinical and epidemiologic studies remain limited compared with systemic drug-induced photosensitivity. Therefore, future research is warranted to better define its incidence, risk factors, and clinical spectrum.

Diagnostic confirmation of drug-induced photosensitivity relies on phototests and photopatch testing; however, these are infrequently performed in routine practice or research [19]. Photopatch testing is primarily used to evaluate contact photoallergy from topically applied medications and sunscreen components. Its utility for diagnosing photo-induced eruptions

caused by systemic medications is not well established, and results may be negative even when a clear causal relationship exists. Interpretation can also be challenging when a systemically administered drug is tested in a topical formulation ^[4]. In our study, no photopatch tests or other photobiological investigations were conducted.

It is essential to distinguish drug-induced photosensitivity from other causes of photosensitive reactions. Photosensitive disorders can be broadly classified into two groups : (1) those caused primarily by solar exposure and (2) photoaggravated disorders. The first group includes polymorphic light eruption, juvenile spring eruption, actinic prurigo, hydroa vacciniforme, solar urticaria, and chronic actinic dermatitis. Certain genodermatoses, such as DNA repair-deficient syndromes, disorders of cornification, Smith–Lemli–Opitz syndrome and porphyrias, also manifest primarily due to sunlight exposure. The second group includes lupus erythematosus, erythema multiforme, atopic eczema, psoriasis, viral exanthemata, pemphigus, dermatitis herpetiformis, and rosacea [42].

The treatment of drug-induced photosensitivity primarily relies on discontinuing the offending medication. When discontinuation is not feasible, sun avoidance and protective measures are recommended. Administering the drug in the evening may reduce the risk, depending on its pharmacokinetic properties [3, 9, 23]. Management can be particularly challenging when patients are on multiple medications or when withdrawal of the causative agent is not possible [3, 10].

Attention must also be given to the potential chronic course of drug-induced photosensitivity and its long-term consequences. Low-grade phototoxicity is increasingly recognized as an important and underappreciated risk factor for skin cancer. Prolonged exposure to photosensitizing medications has been consistently associated with photocarcinogenesis. Although the precise mechanisms remain incompletely understood, the risk appears to be multifactorial, influenced by drug type, cumulative dose, treatment duration, patient age, and individual susceptibility to solar radiation [3, 5]. These observations highlight the need for heightened vigilance and caution when prescribing photosensitizing agents for long-term use.

Strengths and limitations

This is the second nationwide study investigating drug-induced photosensitivity in our country, following the first study conducted in 1980. Internationally, our series represents a relatively large cohort (130 patients) over an extended period (11 years) compared with previously published retrospective studies. Unlike earlier studies, we analyzed both epidemiological and clinical characteristics, identified specific drug classes most frequently implicated, and distinguished cases by underlying mechanism ; phototoxicity or photoallergy, providing a more detailed characterization of these reactions. However, several limitations should be acknowledged. Its retrospective and descriptive design limits the level of drug imputability, as detailed exposure data, rechallenge information, and potential confounding factors could not be fully assessed. Polypharmacy, which is common in older patients, makes it challenging to attribute photosensitivity to a single drug, thereby limiting the reliability of observed associations.

CONCLUSION

In our series, phototoxic reactions predominated over photoallergic reactions. Phototoxicity mainly presented as erythema, while photoallergy was predominantly eczematous. Cardiovascular drugs, anti-infectives, and antineoplastics were the most frequently implicated, with captopril, hydrochlorothiazide, fenofibrate, and atorvastatin among the most common agents. These findings highlight the importance of pharmacovigilance, patient education and preventive measures. Future studies should focus on prospective designs, clearer differentiation between reaction types, photobiological testing, and genetic or mechanistic investigations to better characterize susceptible patients and underlying pathways.

List of abbreviations:

ACE: angiotensin converter enzyme

ADR: Adverse drug reaction

ARBs: Angiotensin II receptor blockers

CNPV: National Pharmacovigilance Center

NSAIDs: non-steroidal anti-inflammatory drugs

UVA: Ultraviolet A

UVB: Ultraviolet B

Author Contributions:

YSM: Writing-original draft; OC and FMZ: Writing-review and editing; AZ: Investigation; GL: Visualization; ID: Formal analysis; SK: Methodology; IA: Supervision; SEA: Validation.

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials:

Data supporting the results of this study are available upon request from the corresponding author.

Ethics Committee Approval and Consent to participate:

This study was conducted using anonymized pharmacovigilance data reported to the National Pharmacovigilance Center (CNPV), Tunisia. According to national regulations, retrospective analyses of anonymized pharmacovigilance reports do not require additional approval from an ethics committee. Therefore, separate ethical approval and informed consent from patients were not applicable.

Human Rights:

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (as revised in 2013).

Consent for Publication:

For figure 2, informed consent for both participation and publication was obtained from the patient.

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Conflicts of Interest:

The authors declare no conflicts of interest regarding this manuscript.

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REFERENCES

- 1 Béani JC. Photodermatoses : photosensibilisations endogènes et exogènes. EMC - Dermatologie. 2021;1-20[Article 98-785-A30]
- 2 Saurat JH, Lachapelle JM, Lipsker D, Thomas L. Peau et soleil. In : Dermatologie et infections sexuellement transmissibles. 5ème édition. Editeur Elsevier Masson SAS (Paris, France) 2008:399-419
- 3 Hofmann GA, Weber B. Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences. J Dtsch Dermatol Ges. 2021 Jan;19(1):19-29
- 4 Blakely KM, Drucker AM, Rosen CF. Drug-Induced Photosensitivity-An Update: Culprit Drugs, Prevention and Management. Drug Saf. 2019 Jul;42(7):827-847
- 5 Di Bartolomeo L, Irrera N, Campo GM, Borgia F, Motolese A, Vaccaro F, et al. Drug-Induced Photosensitivity: Clinical Types of Phototoxicity and Photoallergy and Pathogenetic Mechanisms. Front Allergy. 2022 Jun 20;3:876695
- 6 Montastruc JL. Pharmacovigilance and drug safety: Fair prescribing and clinical research. Therapie 2022;77:261-3
- 7 Abdel-Haq N, Surapaneni V, Seth D, Pansare M, Asmar BI. Voriconazole-Induced Photosensitivity in Children: A Case Report and Literature Review. Glob Pediatr Health. 2014 Dec 1;1:2333794X14562230
- 8 Glatz M, Hofbauer GF. Phototoxic and photoallergic cutaneous drug reactions. Chem Immunol Allergy. 2012 May;97:167-79
- 9 Alrashidi A. Prevalence and prediction of drug-induced photosensitivity [thesis : medecine]. Manchester: The University of Manchester; 2021

- 10 Lugović-Mihić L, Duvančić T, Ferček I, Vuković P, Japundžić I, Ćesić D. Drug-Induced Photosensitivity - a Continuing Diagnostic Challenge. *Acta Clin Croat*. 2017 Jun;56(2):277-283.
- 11 Kahri T. Les photosensibilisations médicamenteuses: A propos de 182 cas [thèse : médecine]. Tunis: Université Tunis El-Manar; 1980
- 12 Huet D. Photodermatoses médicamenteuses : revue de la littérature et analyse des cas notifiés dans la Base Nationale de Pharmacovigilance du 1er Janvier 2010 au 30 Juin 2012. Place du pharmacien d'officine [thèse : pharmacie]. Angers: Université d'Angers; 2014
- 13 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 Nov;36(6):441-51
- 14 Pralong P, Ciszynski M, Moncourier M, Beani JC, Charles J, Leccia MT. Contribution of phototesting in the diagnosis of photodermatoses: Retrospective study of 100 cases. *Photodermatol Photoimmunol Photomed*. 2022 Mar;38(2):99-103
- 15 Elkeeb D, Elkeeb L, Maibach H. Photosensitivity: a current biological overview. *Cutan Ocul Toxicol*. 2012 Dec;31(4):263-72
- 16 Monteiro AF, Rato M, Martins C. Drug-induced photosensitivity: Photoallergic and phototoxic reactions. *Clin Dermatol*. 2016 Sep-Oct;34(5):571-81
- 17 Grosu Dumitrescu C, Jijie AR, Manea HC, Moacă EA, Iftode A, Minda D, Chioibaş R, Dehelean CA, Vlad CS. New Insights Concerning Phytophotodermatitis Induced by Phototoxic Plants. *Life (Basel)*. 2024 Aug 16;14(8):1019.
- 18 Passeron T, Lim HW, Goh CL, Kang HY, Ly F, Morita A, Ocampo Candiani J, Puig S, Schalka S, Wei L, Dréno B, Krutmann J. Photoprotection according to skin phototype and dermatoses: practical recommendations from an expert panel. *J Eur Acad Dermatol Venereol*. 2021 Jul;35(7):1460-1469.
- 19 Stein KR, Scheinfeld NS. Drug-induced photoallergic and phototoxic reactions. *Expert Opin Drug Saf*. 2007 Jul;6(4):431-43
- 20 Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. *Ther Adv Drug Saf*. 2016 Feb;7(1):11-22

- 21 Dkhissi S. Drug-induced photosensitization: management and advice in the pharmacy [thesis: pharmacy]. Amiens: University of Picardie Jules Verne; 2016. ffdumas-01471799
- 22 Photosensitization: origins, mechanisms and management in pharmacies [thesis: pharmacy]. Marseille: University of Aix-Marseille; 2021. ffdumas-03367834
- 23 Korzeniowska K, Cieślewicz A, Chmara E, Jabłecka A, Pawlaczyk M. Photosensitivity reactions in the elderly population: questionnaire-based survey and literature review. *Ther Clin Risk Manag*. 2019 Sep;15:1111-9.
- 24 Rodríguez Granados MT, Abalde T, García Doval I, De La Torre C. Systemic photosensitivity to quinapril. *J Eur Acad Dermatol Venereol*. 2004 Apr;18(3):389-90.
- 25 Viola E, Coggiola Pittoni A, Drahos A, Moretti U, Conforti A. Photosensitivity with Angiotensin II Receptor Blockers: A Retrospective Study Using Data from VigiBase(®). *Drug Saf*. 2015 Oct;38(10):889-94
- 26 Kowalska J, Rok J, Rzepka Z, Wrześniok D. Drug-induced photosensitivity-from light and chemistry to biological reactions and clinical symptoms. *Pharmaceuticals*. 2021 Jul;14(8):1-30.
- 27 Sommer M, Trautmann A, Stoevesandt J. Relief of photoallergy: atorvastatin replacing simvastatin. *J Investig Allergol Clin Immunol*. 2015 Dec;25(2):138-40.
- 28 Rodríguez Pazos L, Sánchez Aguilar D, Rodríguez Granados MT, Pereiro Ferreirós MM, Toribio J. Erythema multiforme photoinduced by statins. *Photodermatol Photoimmunol Photomed*. 2010 Aug;26(4):216-8.
- 29 Götzinger F, Reichrath J, Millenaar D, Lauder L, Meyer MR, Böhm M, et al. Photoinduced skin reactions of cardiovascular drugs-a systematic review. *Eur Heart J Cardiovasc Pharmacother*. 2022 Jun;8(4):420-30.
- 30 Davis AE, Kennelley GE, Amaye Obu T, Jowdy PF, Ghadersohi S, Nasir Moin M, et al. The phenomenon of phototoxicity and long-term risks of commonly prescribed and structurally diverse drugs. *J Photochem Photobiol*. 2024 Feb;19:1-37.
- 31 Zelickson AS. Phototoxic reaction with nalidixic acid. *J Am Med Assoc*. 1964 Nov;190:556-7.
- 32 Zhao J, Liu Y, Jiang X, Guo P, Xu Y, Zhang P, et al. Effect of C-5 position on the photochemical properties and phototoxicity of antofloxacin and levofloxacin: a stable and transient study. *J Photochem Photobiol B*. 2016 Feb;155:122-9.
- 33 Sibaud V. Anticancer treatments and photosensitivity. *J Eur Acad Dermatol Venereol*. 2022 Jun;36 Suppl 6:51-8.

- 34 Lacouture ME, Duvic M, Hauschild A, Prieto VG, Robert C, Schadendorf D, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. *Oncologist*. 2013 Feb;18(3):314-22.
- 35 Ferguson J, Addo HA, Johnson BE, Frain Bell W. Quinine induced photosensitivity: clinical and experimental studies. *Br J Dermatol*. 1987 Nov;117(5):631-40.
- 36 Ljunggren B, Hindsén M, Isaksson M. Systemic quinine photosensitivity with photoepicutaneous cross-reactivity to quinidine. *Contact Dermatitis*. 1992 Jan;26(1):1-4.
- 37 Lisi P, Assalve D, Hansel K. Phototoxic and photoallergic dermatitis caused by hydroxychloroquine. *Contact Dermatitis*. 2004 Apr;50(4):255-6.
- 38 Amichai B, Grunwald MH, Livni E, Halevy S. Photosensitivity due to isotretinoin: a possible allergic mechanism. *J Eur Acad Dermatol Venereol*. 1993 Mar;2(1):27-30.
- 39 Coelho L, Almeida IF, Sousa Lobo JM, Sousa E Silva JP. Photostabilization strategies of photosensitive drugs. *Int J Pharm*. 2018 Apr 25;541(1-2):19-25.
- 40 Wilm A, Berneburg M. Photoallergy. *J Dtsch Dermatol Ges*. 2015 Jan;13(1):7-12.
- 41 Conilleau V, Domp martin A, Michel M, Verneuil L, Leroy D. Photoscratch testing in systemic drug-induced photosensitivity. *Photodermatol Photoimmunol Photomed*. 2000 Apr;16(2):62-6.
- 42 Murphy GM. Diseases associated with photosensitivity. *J Photochem Photobiol B*. 2001 Nov 15;64(2-3):93-8.



Figure 1 : Erythema on the arm



Figure 2: Eczema of the forehead

Table 1: Drugs associated with phototoxicity

Pharmacotherapeutic classification	Drug class	International common denomination	Number of cases	Percentage (%)
Antihypertensive			43	31.7
	Angiotensin-converting enzyme inhibitors	Captopril, Ramipril, Perindopril, Enalapril	17	12.5
	Diuretics	Hydrochlorothiazide, Furosemide	11	8.1
	Angiotensin II receptor blockers	Irbesartan, Valsartan, Losartan, Telmisartan	9	6.7
	Calcium channel	Amlodipine	5	3.7

	blocker			
	Beta-blocker	Bisoprolol	1	0.7
Anti-bacterial			17	12.5
	Anti-tuberculosis	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide	8	5.9
	Cyclins	Doxycycline	5	3.7
	Quinolones	Ciprofloxacin, Levofloxacin	2	1.5
	Macrolides	Clarithromycin, Spiramycin	1	0.7
	Beta lactam	Amoxicillin	1	0.7
Antineoplastic			14	10.3
	Taxanes	Paclitaxel, Docetaxel	6	4.4
	Fluoropyrimidine	Capecitabine, Fluorouracil	3	2.2
	Antifolates	Methotrexate	2	1.5
	Monoclonal antibody	Trastuzumab	2	1.5
	Tyrosine kinase inhibitor	Imatinib	1	0.7
Hypolipidemics			12	8.8
	Statins	Atorvastatin, Rosuvastatin	7	5.1
	Fibrates	Fenofibrate	5	3.7
Non-steroidal anti-inflammatory			6	4.5
	Propionic	Ketoprofen	3	2.4
	Coxib	Celecoxib	1	0.7
	Indole-acetic acid	Indomethacin	1	0.7
	Oxicam	Piroxicam	1	0.7
Antimalarial		Chloroquine, Hydroxychloroquine	6	4.5
Antiepileptic		Carbamazepine, Phenobarbital, Lamotrigine	5	3.7
Anti-fungal		Fluconazole, Voriconazole, Terbinafine	5	3.7
Anti-arrhythmic		Amiodarone	4	2.9
Anti-parasitic		Metronidazole	4	2.9
Anti-psychotics		Fluphenazine, Chlorpromazine	3	2.2
Anti-diabetic		Glimepiride, Metformin	3	2.2
Immunosuppressive		Azathioprine, Pirfenidone	3	2.2

Anti-depressant	Paroxetine	2	1.5
Intestinal anti-inflammatory	Sulfasalazine	2	1.5
Proton pump inhibitors	Omeprazole	2	1.5
Anti-acne	Isotretinoin	1	0.7
Anti-gout	Allopurinol	1	0.7
Anti-rheumatic	Leflunomide	1	0.7
Anti-thyroid	Thiamazole	1	0.7
Carbonic anhydrase inhibitor	Acetazolamide	1	0.7
Total		136*	100

*In 21 cases, more than one drug was suspected

Table 2: Drugs associated with photoallergy

Pharmacotherapeutic classification	Drug class	International common denomination	Number of cases
Antihypertensive			10
	Angiotensin-converting enzyme inhibitors	Captopril, Ramipril	5
	Diuretics	Hydrochlorothiazide, Furosemide	4
	Calcium channel blocker	Amlodipine	1
Hypolipidemics			8
	Fibrates	Fenofibrate	5
	Statines	Atorvastatin	3
Non-steroidal anti-inflammatory			3
	Propionics	Tiaprofenic acid Ketoprofen	2
	Fenamate	Niflumic acid	1
Anti-bacterial			
	Quinolones	Ciprofloxacin	1
	Macrolides	Clarithromycin	1
Antimalarial		Hydroxychloroquine	1
Anti-gout		Allopurinol	1
Anti-fungal		Griseofulvin	1
Anti-parasitic		Metronidazole	1
Anti-psychotics		Olanzapine	1
Total			28*

*In 3 cases, more than one drug was suspected.