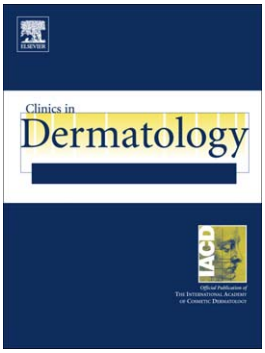

Drug-inducedPhotosensitivity: Photoallergic and phototoxic reactions

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Abstract

Drug-induced photosensitivity refers to the development of cutaneous disease due to the interaction between a given chemical agent and sunlight. Photosensitivity reactions can be classified as phototoxic or photoallergic. Sometimes, there is an overlap between these two patterns, making their distinction particularly difficult for the clinician. We review the drugs, which have been implicated as photosensitizers, the involved mechanism, as well as their clinical presentations. The main topical agents, which cause contact photosensitivity, are the nonsteroidal anti-inflammatory drugs, whereas the main systemic drugs inducing photosensitivity are antimicrobials, nonsteroidal anti-inflammatory agents and cardiovascular drugs. Drug-induced photosensitivity remains a common clinical problem, frequently underdiagnosed.

Introduction

Drug-induced photosensitivity refers to the development of a cutaneous disease due to exposure to a chemical agent and sunlight.[1] The chemical agent can be a topical or systemic drug able to reach the skin. Drug induced photosensitivity frequently occurs in clinical practice, representing up to 8% of reported cutaneous adverse events from drugs.[2] Many drugs, including several classes of antimicrobials, nonsteroidal anti-inflammatories (NSAIDs), cardiovascular agents and even psychotropics have been implicated in photosensitive reactions.

Data suggest that more than 300 drugs are reported to be photosensitizers; however, most of the time the relationship between the drug and sun exposure may not be obvious and the effect of only a few drugs have been well described.[3] This leads to numerous underdiagnosed and under-reported reactions. It is important to establish this relationship in order to remove the offending agent or take adequate measures to prevent adverse effects.

Photosensitive drugs are exogenous chromophores which absorb photons. They are activated upon sun exposure and undergo chemical reactions.[3] The chemical structure of a chromophore determines the wavelengths of radiation that it absorbs. Most photosensitive reactions are caused by ultraviolet A (UVA) rather than ultraviolet B (UVB) radiation.[4] Depending upon the pathophysiologic mechanism, ultraviolet radiation (UVR) can induce an inflammatory reaction (phototoxicity) or a T-cell-mediated reaction (photoallergy).[3]

In an effort to distinguish between both identities, clinical history, physical examination, histology, and some tests such as phototesting and photopatch testing may be

used; however, the distinction can be difficult and most drugs can induce both pathophysiologic patterns.

Photosensitive drug reaction: Phototoxicity VS. Photoallergy

On physical examination of a patient with a photosensitive drug reaction, one expects to see a photodistribution classically involving the face, neck, forearms, and hands, while sparing non-sun-exposed areas, including the breasts and genitalia.[5]

Clinical manifestations of photosensitivity can include the classic pruritic eczematous eruption of photoallergy and the typical exaggerated sunburn eruption of phototoxicity. Several other manifestations are possible e.g. lichenoid eruptions, onycholysis, erythema multiforme, hyperpigmentation, telangiectasia, and even pseudoporphyria in the absence of abnormal porphyrin levels.[5]

A distinction between the two patterns of photosensitivity, photoallergic and phototoxic reactions, may be difficult, but some principles have been established. Photoallergic drug reactions are less common than phototoxic reactions and usually require a minimal exposure to the photosensitizing drugs and prior sensitization.[6] The mechanism is immunologically mediated, a photoproduct acts as a hapten or as a complete antigen to generate a type-IV hypersensitivity reaction, and cross-reactions between similar drugs can occur.[4] Usually, it develops 24 hours or more after the initial exposure and it resembles an eczematous dermatitis that may spread beyond the sun-exposed skin. After discontinuation the photoallergy resolves; however, in rare cases, it can persist and evolve into chronic actinic dermatitis.[6] Histologically, epidermal spongiosis, vesiculation, exocytosis of lymphocytes into the epidermis, and perivascular inflammatory infiltrates are seen. Prior

contact with the drug may not be necessary, if the patient has previously been sensitized by contact with a similar molecule.[4]

Phototoxic drug reactions, besides happening much more frequently, will supposedly occur in all individuals exposed to high enough doses of either the drug or the radiation at the appropriate wavelengths.[5] The phototoxic reaction is the result of direct tissue and cellular injury by a photoproduct.[4] Usually, it is dose dependent and does not require prior sensitization.[6] It occurs minutes to hours after sunlight exposure and manifests clinically as exaggerated sunburn with associated burning and itching sensations localized on sun-exposed areas. Histologically, this reaction displays epidermal keratinocytes necrosis with dermal lymphocytic and neutrophilic infiltrate.[5]

In clinical practice, the two testing methods that have proven useful to differentiate the photosensitive mechanism are phototesting and photopatch testing.

- Phototesting involves the use of a solar simulator with the aim to determine whether the minimal erythema dose (MED) (exposure to UVR leading to the first faint reddening of the skin) is reduced in the presence of the agent. It is done in a number of shielded and unshielded areas on the upper back of the patient while taking and then not taking the suspected drug.[5]
- Photopatch testing is indicated for the evaluation of photoallergy.[6] It involves the application of drugs on the patient's back and then occlusion. Twenty-four hours later, the patches are uncovered and irradiated with a dose of UVR below the MED. Twenty-four hours additionally, the irradiated areas are examined, and if there is a reaction only at the irradiated site, it is suggestive of a photosensitive reaction. The use of photopatch testing in clinical practice is largely limited to testing topical agents and compounds of sunscreens to

diagnose photocontact dermatitis. Its use for the diagnosis of photo-induced cutaneous eruptions due to systemic medication has not been validated.[5]

Most photosensitivity drug reactions resolve with sun avoidance and drug discontinuation.[7] Patients who are unable to discontinue the offending agent will need topical steroids and protective measures are available to minimize symptoms, including broad-spectrum sunscreen and protective clothing. Currently there is increasing concern about photosensitive premarketing studies, making photochemical reactivity screening an important part of drug development.[6]

Photosensitive Drugs

Topical Drugs

Miscellaneous topical drugs

Topical agents (Table 1) may cause two types of photo-related reactions: photo-contact allergic dermatitis and topical phototoxicity.

Several topical drugs have been implicated in photo-contact allergic dermatitis e.g. acyclovir, dibucaine injection, hydrocortisone, chlorpromazine gel and sunscreens.[8–11]

The majority of sunscreens that can produce a photoallergic reaction include p-aminobenzoic acid (PABA), benzophenones, cinnamates, salicylates and octocrylene; however, newer sunscreens, such as Mexoryl SX, Tinosorb M and Tinosorb S, are photostable molecules and are rarely associated with photosensitive reactions. Only one case of photoallergy has been reported due to Mexoryl SX.[12]

Among suncreens, oxybenzone is still the most frequently used UVR filter responsible for positive photopatch tests.[13]

Regarding topical phototoxicity, furocoumarins and coal tar have been implicated. Photoactive furocoumarins such as bergapten, 5- and 8-methoxypsoralen, are compounds synthetized by plants and used in folk medicine, photochemotherapy and in cosmetic industry. A phototoxic reaction can also occur with inadvertent contact with these plants. When skin is exposed to furocoumarins and to ultraviolet light, a photosensitive reaction may occur, known as phytophotodermatitis. Plants rich in furocoumarins belong mainly to the family *Umbelliferae*, *Rutacea* and *Moracea.* The most typical pattern of phytophotodermatitis is dermatosis bullosa striada pratensis, characterized by linear streaks beginning within 24-48 hours with prickling with erythema and, later, painful vesicles and bullae. It may continue as linear hyperpigmentation.[3,14]

Coal tar can result in a phototoxic reaction, characterized by immediate burning sensation, followed by a wheal response in 1 hour and erythema in 24-48 hours, if the patient is exposed to sunlight.[15]

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Benzydamine is available for application to the oral and genital mucosae.[16] It may cause photoallergic contact dermatitis, photosensitivity at distant sites, and when used orally, can induce cheilitis and submental dermatitis.[16,17]

Although studies suggest phototoxicity, ketoprofen mainly causes photoallergic reactions.[18] Ketoprofen was found to be responsible for 82% of photoallergy reactions attributable to topical NSAIDs with some severe reactions

described in literature.[19] Clinically, this dermatitis usually presents as edema, bullae, dermatitis, or erythema multiforme, occasionally extending beyond the area of application.[20] Reactions may occur on sun exposure with no apparent further drug application, explained by the persistence of the drug in the skin.[18] Cross-reactions occur with tiaprofenic acid, suprofen, sunscreens containing mainly oxybenzone, and fenofibrate.[3,21]

Piroxicam can induce a systemic photoallergy.[22] Commonly, the individuals have been previously sensitized with thimerosal.[3] Clinical manifestations include: acute dermatitis, dyshidrosis, scattered erythematous papules, and vesicles on the face and dorsum of the hands.[23,22]

Diclofenac, a commonly used analgesic, has been associated with an acute vesicular eczematous photoallergic dermatitis.[24] Cross-reactions have been reported with topical aceclofenac.[25]

Oral drugs

ANTIMICROBIALS

Within the antimicrobials group, photosensitivity reactions have been reported most frequently from tetracyclines, fluoroquinolones, and sulfonamides (Table 2).

Tetracyclines

Tetracyclines are one of the best known causes of photo-induced drug reactions. Doxycycline and demeclocycline are the most frequent sensitizers, with demeclocycline being the strongest in the group.[6] Doxycycline has been reported to cause classic phototoxic eruptions and photo-onycholysis (Figure 1).[26,27] Tetracycline

is known to manifest exaggerated sunburn, photo-onycholysis, pseudoporphyria, solar urticaria, and frequently marked residual pigmentation.[28,29]

Despite lymecycline and minocycline not being significant photosensitizers, they have recently been reported to cause photo-onycholysis.[29,30]

Fluoroquinolones

The most frequently reported photosensitive effects of nalidixic acid, the first fluoroquinolone, include systemic phototoxic eruptions, porphyria cutanea tarda, and pseudoporphyria.[28]

The introduction of new fluoroquinolones took place in the 1980's, and it has become clear that they still exhibit varying degrees of photosensitivity.[28] Clinical manifestations of phototoxicity range from mild erythema of sun-exposed areas to severe bullous eruptions.[28,31] Several reviews have shown that fluoroquinolones have phototoxic, photoallergic, and photomutagenic outcomes, both *in vitro* and *in vivo.*[32]

The most important determinant of fluoroquinolone photosensitivity is the halogenation at the C-8 position.[31–34] Lomefloxacin and sparfloxacin with a C-8-fluorine substituent and clinafloxacin with a C8-chlorine substituent exhibit a greater incidence of phototoxic reactions (Figure 2).[31–34] In contrast, the presence of a methoxy group at this position increases the photo-stability of gatifloxacin and moxifloxacin.[31–34]

Levofloxacin and ciprofloxacin, two of the most currently used quinolones, have a relatively low incidence of phototoxic-potential.[31,33,34]

The overall phototoxic-potencial ranking of certain quinolones, from the greatest to the least, follows: lomefloxacin, fleroxacin, clinafloxacin, sparfloxacin, enoxacin, pefloxacin, ulifloxacin, ciprofloxacin, grepafloxacin, gemifloxacin,

levofloxacin, norfloxacin, ofloxacin, trovafloxacin, gatifloxacin, and moxifloxacin.[28,31–34]

Usually, fluoroquinolones produce phototoxic reactions, although there are a few reports of photoallergy with enoxacin and lomefloxacin.[35,36] While sparfloxacin was implicated in a lichenoid reaction, photoallergy was not confirmed.[37] Norfloxacin was reported to induce a generalized erythematous subcorneal pustular drug eruption.[38]

Third- Generation Cephalosporins

Third-generation cephalosporins have been rarely implicated in photosensitization; however, cefotaxime was reported to cause photodistributed telangiectasia and ceftazidime an increased susceptibility to sunburn.[39,40]

Antimalarials

Among antimalarials, quinine and quinidine cause photosensitive dermatosis with several different morphologic presentations: edematous, eczematous, lichenoid, photo-onycholytic, and livedoid purpuric eruptions.[41–45] Experimental data suggest that photoproducts from irradiated quinine and quinidine can be identical, justifying the cross-reaction in the photopatch testing.[41]

Anti-tuberculosis medications

Anti-tuberculosis medications, including isoniazid and pyrazinamide, have been reported to cause a lichenoid eruption.[46,47]

Sulfonamide derivatives

Despite sulfonamide antimicrobials being relatively safe from photosensitivity, sulfur-containing diuretics and antidiabetics drugs are more common offending agents.[28] Cotrimoxazole has been implicated as a photosensitizer, and the sulfamethoxazole component is believed to be responsible.[48] Dapsone has also been rarely implicated as a photosensitizer.[49] Sulfasalazine has been reported to produce diffuse hyperpigmentation on photo-exposed areas.[50]

Antifungals

Some antifungals known to cause photosensitivity include voriconazole, itraconazole, ketoconazole, and griseofulvin.[51–54]

Voriconazole photo-induced dermatologic findings include sunburn-like erythema, hand hyperpigmentation, linear papulo-vesicular lesions, exfoliative dermatitis, discoid lupus erythematosus, dermatoheliosis, and occasionally cheilitis and pseudoporphyria.[54–56] Most reactions occur in patients receiving long-term therapy for several immunocompromised states.[54] There are reports of subsequent development of squamous cell carcinoma and melanoma in the areas affected by the photosensitive eruption.[57]

AntiRetrovirals

In the antiretroviral group, efavirenz has been reported to cause a photodistributed papulosquamous annular erythema in HIV patients.[58,59]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

The NSAIDs are a heterogeneous group, in which photosensitivity has been reported most often for benoxaprofen and piroxicam. Benoxaprofen was removed from the market, as its phototoxic reaction incidence was up to 50%.[60] A case of subsequent development of melanoma after photosensitization was recently reported.[61] Other drugs implicated as photosensitizers include ketoprofen, tiaprofenic acid, naproxen, and nabumetone (Table 3).[62–64] Among the most commonly used, naproxen appears to have the most photosensitizing potential.[62] Usually, it presents as pseudoporphyria, although there are reported cases of photodistributed erythema multiforme and lichenoid photodermatitis.[65,66] Celecoxib, a recent NSAID, has been reported to cause photoallergic and pseudophorphyria reactions.[67,68] Ibuprofen is generally not considered to be phototoxic, even though there is a case report describing a phototoxic reaction.[69]

ANTIHYPERTENSIVES

Diuretics

In the thiazide diuretics group, hydrochlorothiazide (HCTZ) is the most photosensitive drug (Table 4). Clinical manifestations include an exaggerated sunburn reaction, erythema, dermatitis, lichenoid eruption, subacute cutaneous lupus erythematosus (SCLE), pseudoporphyria, photo-onycholysis, and photoleukomelanoderma.[70–73] Indapamide has been reported to cause photo-onycholysis.[74]

Furosemide has been reported to cause a bullous photo-eruption, mainly in high doses.[75]

There is a clinical case of triamterene induced-photosensitivity reported.[76]

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB)

Among the ACE inhibitors, captopril, ramipril, quinapril and enalapril have been reported to cause photosensitive reactions.[77–80] Captopril was reported to cause a follicular mucinosis as a photoallergic manifestation.[77]

The only ARB reported to cause photosensitivity was valsartan.[81]

Calcium Channel Blockers (CCB)

Among calcium channel blockers, amlodipine and nifedipine, have been reported to cause photodistributed facial telangiectasia.[82,83] Diltiazem has been found to cause photodistributed hyperpigmentation, photosensitivity, and photoallergic dermatitis.[83,84] Cross reaction between the CCBs is known.[83]

Other antihypertensives

Among β-blockers, tilisolol was reported once in the literature to cause photosensitivity.[85] Rilmenidine was implicated in an erythematous and swelling reaction with a photodistributed pattern.[86] Methyldopa was reported to cause an erythematous pruritic papulovesicular eruption.[87]

ANTIARRHYTHMICS

Amiodarone

The incidence of amiodarone photosensitive eruptions ranges from 25 to 75%. Phototoxic, photoallergic reactions, and hyperpigmentation are the main skin

changes induced by amiodarone.[88] After long-term exposure, amiodarone may induce a distinctive blue-grey pigmentation on sun-exposed areas in less than 10% of patients.[89] Photosensitivity may even occur months after the withdrawal of amiodarone due to its long elimination time. Full remission of photo-induced pigmentation is commonly achieved over several months to years.[88] There is a possible connection between amiodarone-induced photosensitivity and the subsequent development of basalioma.[90]

Dronaderone, a new antiarrhythmic, has been recently reported to cause diffuse erythematous phototoxic eruptions.[91]

CHOLESTEROL-LOWERING AGENTS

Cholesterol-lowering agents have been rarely reported as photosensitizers. Simvastatin may cause chronic actinic dermatitis, while torvastatin may cause erythema with edema.[92,93] Photodistributed erythema multiforme may occur with simvastatin and pravastatin.[94] In addition, fenofibrate has been reported to cause an eczematous, lichenoid photosensitivity.[95,96]

PSYCHOTROPICS

Antipsychotics

Almost all phenothiazines are strong photosensitizers (Table 5). Chlorpromazine has been more commonly implicated, although thioridazine, fluphenazine, and perphenazine have also been associated with photo-sensitivity.[97–99] Classic phototoxic reactions and photoallergic contact dermatitis have been reported for chlorpromazine and thioridazine.[100–104] Either chlorpromazine or

thioridazine, used in high dosages for long-term therapy, may produce a slate-grey to violaceous hyperpigmentation on sun-exposed areas.[100] Photo cross-reaction was documented between chlorpromazine and other phenothiazines.[105] Flupenthixol was reported to cause erythematous allergic eruptions.[106]

Olanzapine and clozapine are not strong photosensitizers; however, olanzapine has been reported to cause photo-onycholysis, and clozapine was reported to cause a photosensitivity dermatitis.[107,108]

Antidepressants

Photosensitivity is a relatively rare adverse effect from tricyclic antidepressants.[100] Although protriptyline, amitryptiline, imipramine, clomipramine and desipramine have been implicated as photosensitizers.[109–111] There are few reports of hyperpigmentation on sun-exposed areas due to amitriptyline.[100] The most common cutaneous adverse reaction to imipramine is photosensitivity. Reactions include photodistributed erythema and slate-grey hyperpigmentation after long-term exposure.[109,112] Clomipramine has been implicated in photoallergic dermatitis.[110] There is also a reportd case of blue-gray pigmentation on sun-exposed surfaces related to desipramine.[111]

Selective serotonin reuptake inhibitors are not considered potent photosensitizers, even though escitalopram, paroxetine, fluvoxamine, fluoxetine, and sertraline have been reported to cause a photo-distributed erythematous reaction.[113] Citalopram may cause a photo-distributed hyperpigmentation, and recently it was implicated in a case report of SCLE.[114]

Regarding serotonin-noradrenaline reuptake inhibitor, venlafaxine was reported to cause photodistributed telangiectasia.[115]

Phenelzine, a monoamine oxidase inhibitor, has been reported only once as a photosensitizer.[116]

Anxiolytics

Alprazolam, a benzodiazepine, was reported to cause a photo-distributed pruritic erythema.[117] Chlordiazepoxide is known to cause mainly photoallergic eczematous eruptions.[118]

CHEMOTHERAPEUTIC AGENTS

Among antineoplastic drugs (Table 6), photosensitivity to vandetanib and vemurafenib is common. There is an incidence of photosensitive eruptions in 37% of patients taking vandetanib for 8 weeks.[119] It can manifest as exaggerated sunburn, erythematous bullous or lichenoid eruption, hyperpigmentation, and less frequently as photo-induced SCLE or erythema multiforme.[119–121] The cases reported in literature are closer to a phototoxic mechanism; however, it has also been described as a case of photo-allergic reaction.[122]

Phototoxicity is a common side effect of vemurafenib, a serine/threonine protein kinase B-raf inhibitor, developed for the treatment of late-stage melanoma.[123,124] It is known to be triggered mostly by UVA radiation and resolves rapidly after drug discontinuation.[124,125]

Imatinib has been reported to cause a photo-induced dermatitis with an oral lichenoid reaction and an exaggerated sunburn in patients being treated for chronic myelogenous leukaemia.[126,127]

Fluorouracil has been reported to cause sunburn reactions, photodistributed hyperpigmentation, and SCLE.[128–130] Capecitabine is an alternative choice to fluorouracil, although it may cause a photodistributed lichenoid eruption.[131] Tegafur may cause a lichenoid and eczematous photodistributed eruptions.[132]

Paclitaxel has been reported to cause photodistributed erythema multiforme, photo-onycholysis, photo recall phenomenon, SCLE, and elevated photoporphyrin.[133,134] Hydroxyurea has been associated with a photodistributed granulomatous reaction and can lead to a phototoxic dermatosis.[135] Dacarbazine has been reported to cause phototoxic reactions, while vinblastine was once reported to cause a photodistributed vesicular eruption.[136,137,138] Epirubicin can create a bullous photoeruption.[139] Methotrexate is not a real photosensitizer; however, it causes radiation recall phenomena, which can be misunderstood as a photosensitive reaction.[140]

MISCELLANEOUS MEDICATIONS

Among systemic retinoids, etretinate and isotretinoin have been associated with an increased susceptibility to sunburn and photoleukomelanoderma.[141,142]

Contraceptive hormone, ethinylestradiol, has been rarely implicated as a photosensitizer.[143,144] There is a case of pseudoporphyria associated only with the use of oral contraceptive pills (OCP) and natural sun exposure.[144]

Ranitidine has been reported to cause papulosquamous eruptions on sun-exposed area, while carbamazepine and clopidogrel have been reported to cause a photosensitive lichenoid eruption.[145,146,147] Recently, flutamide has been reported to cause vitiliginous lesions as sequellae of flutamide-induced photosensitive dermatitis.[148–150]

Conclusions

Drug-induced photosensitivity remains a frequent clinical concern. Among the most common photosensitizers such drugs as antimicrobials, NSAIDs, amiodarone, and psoralens. Although some classes are more frequently associated with photosensitive reactions, it is prudent to consider that almost any medication can produce a photosensitive reaction, and frequently the majority of mild episodes pass either unnoticed or it is assumed to be a mild sunburn by the patient. Possibly, only severe photosensitive cases are reported to the family physician or referred to the hospital. Consequently, it has been suggested that there is a higher incidence of drug-induced photosensitivity cases than those reported in literature. Drug induced photosensitivity should be considered as a diagnostic hypothesis each time a patient presents with a skin eruption and history of drug intake combined with light exposure. Additionally, diagnostic tools, including photopatch testing and phototesting, may help to establish the causative agent.

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Table 1. Topical drugs reported to cause photosensitive reactions

Class	Subclass	Drug	Phototoxic reaction	Photoallergy reaction
AINES		Benzydamine, Piroxicam, Diclofenac		X
		Ketoprofen	X	X
Miscellaneous		Acyclovir		X
		Dibucain		X
		Hydrocortisone	X	X
		Fenofibrate		X
		Coal Tar	X	
		Benzoyl peroxide	X	
		Benzocaine	X	
		Erythromycin	X	
		Halogenated salicylanilides	X	X
		Chlorpromazine		X
Plants	Umbelliferae	*Ammi majus, Apium graveolens* (celery), *Patinaca sativa* (parsnip), *Petroselinum crispum* (parsley), *Heracleum mantegazzianum* (giant hogweed)	X	X
	Rutacea	*Citrus spp, Citrus aurantica v. bergamia* (bergamot), *Citrus aurantifolia* (lime), *Citrus limon* (lemon), *Ruta graveolans* (common rue), *Dictamus albus* (burning bush)	X	X
	Moracea	*Ficus carica* (fig)	X	X
Sunscreens	Benzophenones	Oxybenzone, sulisobenzone, Mexenone		X
	Others	Dibenzoylmethanes, Cinnamates, PABA, Salycilates, Octocrylene, Mexoryl SX		X

Table 2. Systemic antimicrobials reported to cause photosensitive reactions

Subclass	Drug	Phototoxic reaction	Photoallergy reaction
Tetracyclines	Doxycycline, Demeclocycline Minocycline, Tetracycline, Lymecycline	X	
Fluoroquinolones	Nalidixic acid, Pipemidic acid Oxolinic, Rosoxacin	X	
	Norfloxacin, Lomefloxacin	X	X
	Enoxacin		X
	Ciprofloxacin, Levofloxacin Sparfloxacin, Gatifloxacin Grepafloxacin, Trovafloxacin Clinafloxacin, Gemifloxacin Fleroxacin, Perfloxacin Ulifloxacin, Ofloxacin	X	
	Moxifloxacin	No	No
3rd Generation Cephalosporins	Cefotaxime, Ceftazidime	X	
Antimalarials	Quinine, Quinidine	X	X
Anti-tuberculosis medications	Isoniazid, Pyrazinamide	X	
Sulfonamides derivates	Cotrimoxazole, Dapsone Sulfasalazine	X	
Antifungals	Voriconazole, Itraconazole Ketoconazole, Griseofulvin	X	
	Fluconazole	No	No
AntiRetrovirals	Efavirenz	X	X

Table 3. Systemic nonsteroidal anti-inflammatory drugs reported to cause photosensitive reactions

Class	Drug	Phototoxic reaction	Photoallergy reaction
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Benoxaprofen, Naproxen, Nabumetone, Ibuprofen	X	
	Suprofen, Oxybenzone		X
	Ketoprofen, Tiaprofenic acid	X	X
	Piroxicam, Benzydamine Etofenamate, Diclofenac		X
	Aceclofenac	X	X
	Celecoxib	X	X

Table 4. Systemic cardiovascular drugs reported to cause photosensitive reactions

Class	Subclass	Drug	Phototoxic reaction	Photoallergy reaction
Antihypertensives	**Diuretics**	Hydrochlorothiazide	X	X
		Indapamide, Furosemide, Triamterene	X	
	ACEI and ARB	Captopril, Ramipril, Enalapril, Valsartan		X
		Quinapril	ND	ND
		Enalapril		X
		Valsartan	ND	ND
	Calcium Channel Blockers	Amlodipine, Nifedipine	X	
		Diltiazem	X	X
	Others	Tilisolol	ND	ND
		Rilmenidine	X	
		Methyldopa		X
Antiarrhythmics		Amiodarone	X	X
		Dronaderone	X	
Cholesterol-lowering drugs	HMG-CoA reductase inhibitors	Simvastatin		X
		Atorvastatin	X	
		Pravastatin	ND	ND
		Fenofibrate		X

ND – Drug implicated as photosensitizer without pathophysiological mechanism defined

ACEI – Angiotesin-converting enzyme inhibitors

ARB- angiotensin receptor blockers

Table 5. Systemic Psychotropic drugs reported to cause photosensitive reactions

Subclass	Drug	Phototoxic reaction	Photoallergy reaction
Antipsychotics	Chlorpromazine, Thioridazine, Fluphenazine, Trifluoperazine, Perphenazine, Perazine	X	X
	Flupenthixol		X
	Olanzapine	ND	ND
	Clozapine	ND	ND
Antidepressants	Protriptyline	X	
	Amitryptiline		X
	Imipramine, Desipramine	ND	ND
	Clomipramine		X
	Escitalopram	X	
	Citalopram, Paroxetina, Fluvoxamine	X	X
	Fluoxetine	X	
	Sertraline		X
	Venlafaxine	X	
	Phenelzine	ND	ND
Anxiolytics	Alprazolam	X	
	Chlordiazepoxide		X

ND – Drug implicated as photosensitizer without pathophysiological mechanism defined

Table 6. Other systemic drugs reported to cause photosensitive reactions

Class	Drug	Phototoxic reaction	Photoallergy reaction
Chemotherapeutic Agents			
	Vandetanib	X	X
	Imatinib	X	
	Fluorouracil	ND	ND
	Capecitabine	ND	ND
	Tegafur	X	X
	Paclitaxel	ND	ND
	Hydroxyurea	X	
	Dacarbazine	X	
	Vinblastine	X	
	Epirubicin	ND	ND
	Vemurafenib	X	
Miscellaneous drugs	Retinoids	X	
	Ethinylestradiol	X	
	Ranitidine	X	
	Carbamazepine	ND	ND
	Clopidogrel	ND	ND
	Flutamide	ND	ND
	Sulfonamides	X	X
	Sulfonylureas	X	X

ND – Drug implicated as photosensitizer without pathophysiological mechanism defined

Figure 1 – Acute phototoxic reaction from doxycycline, sparing the sunshade areas.

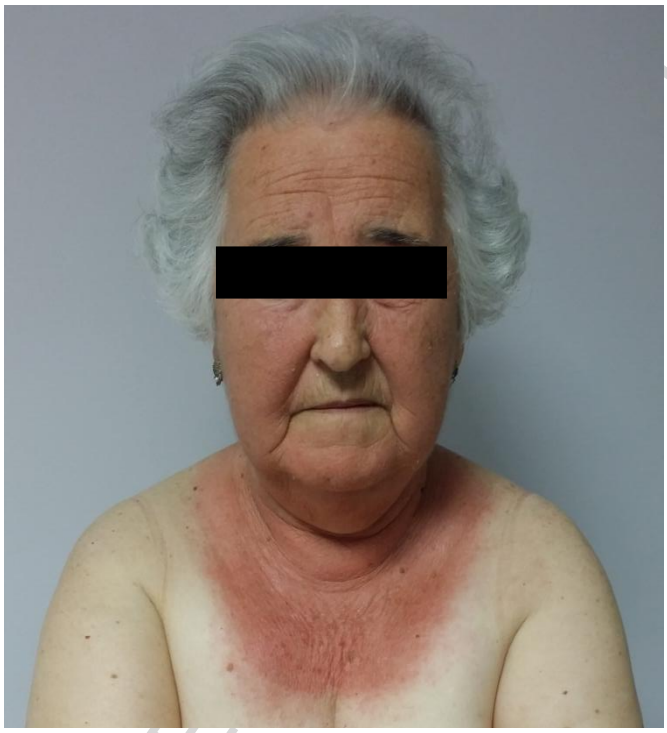

Figure 2 – Photosensitivity from lomefloxacin, lesions on sun-exposed areas (a) V of the neck and (b) forearms.