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Drug-Induced Photosensitivity
Culprit Drugs, Management and Prevention

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Contents

Abstract

Photo-induced drug eruptions are cutaneous adverse events due to exposure to a drug and either ultraviolet or visible radiation. Based on their pathogenesis, they can be classified as phototoxic or photoallergic drug eruptions, although in many cases it is not possible to determine whether a particular eruption is due to a phototoxic or photoallergic mechanism.

In this review, the diagnosis, prevention and management of drug-induced photosensitivity are discussed. Diagnosis is based primarily on the history of

drug intake and the clinical appearance of the eruption, primarily affecting sun-exposed areas of the skin. Phototesting and photopatch testing can be useful adjuncts in making a diagnosis. The mainstay of management is prevention, including informing patients of the possibility of increased sun sensitivity and the use of sun protective measures. However, once the eruption has occurred, it may be necessary to discontinue the culprit medication and treat the eruption with a potent topical corticosteroid. Drugs that have been implicated in causing photosensitive eruptions are reviewed. Tetracycline, doxycycline, nalidixic acid, voriconazole, amiodarone, hydrochlorothiazide, naproxen, piroxicam, chlorpromazine and thioridazine are among the most commonly implicated medications. We review the medical literature regarding evidence for the culpability of each drug, including the results of phototesting, photopatch testing and rechallenge testing.

Photo-induced drug eruptions (PIDEs), also referred to as photosensitive drug eruptions, represent 8% of reported cutaneous adverse events from drugs.[1] PIDEs occur after exposure to a drug and either ultraviolet (UV) or visible radiation. A drug eruption is considered photosensitive if it occurs only in the context of radiation exposure. Exposure to the drug can occur topically or systemically, but in order for the eruption to occur, the drug or one of its metabolites must be present in the skin at the time of exposure to the radiation. Additionally, the drug and/or its metabolites must be able to absorb either visible or UV radiation. UVA radiation, which penetrates deeper into the dermis than UVB, is most commonly implicated in photosensitive drug eruptions, but UVB and visible light have also been involved.

Classically, PIDEs are classified based on their proposed mechanism of action into photoallergic and phototoxic reactions. Attempts to distinguish the two can be made using clinical history and physical examination, as well as histology and tests such as phototesting and photopatch testing. However, the distinction between phototoxicity and photoallergy can be difficult to make and, regardless, does not usually affect management.

In order to be considered a photoallergic drug eruption, the reaction must meet all the criteria for a PIDE in addition to demonstrating an immune-mediated mechanism for the reaction. These reactions do not occur in all persons exposed to the drug and to radiation – each individual's immune system may or may not interact with the drug. Clinically, a predominantly eczematous eruption is seen. This correlates with changes in histology identical to those seen with allergic contact dermatitis such as epidermal spongiosis, vesiculation, exocytosis of lymphocytes into the epidermis and a perivascular inflammatory infiltrate.[2]

Phototoxic drug eruptions are not immune-mediated and as such will occur in all individuals exposed to high enough doses of both drug and radiation at the appropriate wavelengths. They are thought to occur much more frequently than photoallergic reactions. Clinically, the eruption appears as an exaggerated sunburn with associated burning and itching sensations. Histologically, necrotic keratinocytes are seen, along with a dermal lymphocytic and neutrophilic infiltrate.[3] However, both phototoxic and photoallergic drug eruptions may have a dermatitic appearance.

In this article we review the diagnosis of PIDEs and culprit drugs, as well as prevention and management of PIDEs. We have not included reactions to topically administered drugs, including sunscreens, and instead focus on reactions to systemically administered medications. Drugs that cause photosensitivity as part of their desired mechanism of action, e.g. psoralens, have also been excluded.

1. Diagnosis

The diagnosis of PIDEs is largely based on a detailed clinical history and physical examination.

Clinical history should focus on the medication history, with special attention given to the temporal relationship of the eruption with the starting of new medications. Additionally, a general review of systems should be performed to screen for diseases associated with photosensitivity, such as systemic lupus erythematosus.

On physical examination, one would expect to see a photodistributed eruption. Classically, this involves the face, the V of the neck, forearms and hands. Photodistributed eruptions generally spare non-sun-exposed sites, in particular 'doubly covered' areas such as the genital area and breasts. More subtle signs of photosensitivity include sparing under the chin, lower lip and behind the ears as these are relatively protected from solar radiation.

PIDEs can take many different forms. As mentioned, photoallergy classically presents with a pruritic eczematous eruption while phototoxicity classically presents as a burning or painful intense sunburn-like eruption. Photoallergy appears to be much less common than phototoxicity. Other manifestations of photosensitivity can include lichenoid eruptions, onycholysis, erythema multiforme, hyperpigmentation and telangiectasia. PIDEs that manifest as blistering reactions on the hands and feet associated with skin fragility are known as pseudoporphyria, given their resemblance to porphyria cutanea tarda. Pseudoporphyria occurs in the absence of abnormal porphyrin levels. Although the mechanism by which drugs induce pseudoporphyria is not well understood, there is a separation at the subepidemal level that leads to the formation of blisters. Other cutaneous reactions to drugs that result in photosensitivity include drug-induced pellagra and drug-induced lupus erythematosus.

While multiple assays, both *in vitro* and *in vivo*, have been developed to either predict the photosensitizing potential of drugs or to assess a drug's photosensitizing effects on an individual patient, this has been more successful for phototoxicity than for photoallergy. One *in vitro* model of phototoxicity assessed the viability of 3T3 fibroblasts after exposure to a number of different compounds and UVA irradiation. It was able to distinguish, in 19 of 20 compounds, those with known phototoxicity from non-phototoxic compounds.[4] Another model used Chinese hamster fibroblasts to assess the phototoxicity of eight fluoroquinolones, comparing the *in vitro* results with clinical data obtained from phototesting human volunteers both on and off these medications. The *in vitro* assay could discriminate the phototoxic compounds from the non-photosensitizers.[5] In clinical practice, the two testing methods that have proved useful are phototesting and photopatch testing.

Phototesting involves the use of artificial UVA and UVB radiation sources to determine the minimal erythema dose (MED) for a patient while taking and then not taking the suspected drug. The MED is the lowest dose of radiation required to produce uniform erythema on the exposed patch of skin. If the MED is lower while the patient is on the drug, this supports its culpability in a PIDE. Ideally, a rechallenge can also be undertaken, where the patient is instructed to resume taking the drug after it had initially been discontinued. The patient can then be phototested again, determining the MED again while on the medication. The patient can also expose themselves to sunlight while they are taking the drug again to see if the skin eruption recurs.

Photopatch testing involves the duplicate application of medications, compounded in either petrolatum or alcohol, to a patient's back. The patches are covered immediately after application. After 24 hours, one set of patches is uncovered and irradiated with a dose of UVA below their MED. By using a low dose of UVA, often 5 J/cm^2, phototoxic reactions may be avoided, while photoallergic reactions would still occur.[6] Twenty-four hours later, the irradiated and non-irradiated sites are examined for erythema, oedema and vesiculation. If there is a reaction only at the irradiated site, it is suggestive of a PIDE. If there are equal reactions at both the irradiated and non-irradiated sites, it is suggestive of an allergic contact dermatitis to the medication. If there is a reaction at both sites, i.e. with and without exposure to irradiation, but the reaction is greater at the irradiated site, there may be both a contact dermatitis and a photocontact eruption. Difficulties in interpretation of

a positive reaction only at the irradiated site may arise as a systemic medication, applied topically, may induce a phototoxic reaction. However, if the result of the testing is used to establish whether the eruption is photo-induced, and not whether the mechanism is photoallergic or phototoxic, then the testing can be useful.

While it can be useful in some cases, photopatch testing is generally performed only for a limited number of medications. Its use in clinical practice is largely limited to testing for topically applied medications and components of sunscreens to diagnose photocontact allergy. Quinine and chlorpromazine are among the systemic medications for which photopatch testing is routinely performed, but it can be conducted for any medication. Photopatch testing for the diagnosis of photo-induced cutaneous eruptions due to systemic medication has not been validated and may be negative even in situations where the causative relationship between the drug and the photo-induced eruption is clear.[7]

Photoscratch testing is a similar but less commonly used testing method that involves scratching the skin with a needle containing the tested compound rather than just applying the compound to the surface of the skin.

2. Photosensitizing Drugs

In his 2002 review, Moore[8] describes very well the challenges in ascertaining the incidence of PIDEs. Adverse drug reporting databases largely underreport the incidence of these reactions, particularly for drugs that have been on the market for some time and are already known photosensitizers. The medical literature contains some studies on the incidence of PIDEs from various medications, and is also a source for case reports. However, given the widespread use of these medications and the scant reporting of PIDEs, it is impossible to estimate the true incidence of PIDEs accurately. The literature describing PIDEs from systemic medication predominantly consists of case reports and case series, not randomized controlled trials. More randomized, double-blind, placebo-controlled trials of possible photosensitizing medications, using phototesting to detect changes in the MED of UVA due to the medication, would add to the evidence concerning a drug's photosensitizing potential.

In this review, we discuss the drugs that have been reported, in the English-language medical literature, to cause clinical photosensitivity. To identify articles about drug-induced photosensitivity, a literature search was conducted in PubMed using the search terms 'drug induced photosensitivity', 'drug induced photoallergy' and 'drug induced phototoxicity'. Once the articles were obtained, we examined the reference list of each paper to identify other articles of interest.

Table I contains a list of medications that, in our opinion, are common causes of photosensitivity. Tables II–IX list medications, divided by therapeutic class, that have been reported to cause photosensitivity. For each medication listed, the evidence for its culpability in causing a PIDE is given, whether phototesting, photopatch testing or rechallenge testing were positive. We consider photopatch testing and rechallenge testing to be the strongest evidence available.

2.1 Antimicrobials

2.1.1 Tetracyclines

Among the various classes of antimicrobials, tetracyclines are perhaps the best known causes of PIDEs. Tetracycline and doxycycline, two tetracycline antibiotics still in common use today, have been reported to cause phototoxic dermatoses. Minocycline is generally not considered to be a significant cause of photosensitivity, but photo-onycholysis has been reported.[79] Tetra-

Table I. Common photosensitizing medications according to the authors' experience and literature review (in alphabetical order)

Amiodarone
Chlorpromazine
Doxycycline
Hydrochlorothiazide
Nalidixic acid
Naproxen
Piroxicam
Tetracycline
Thioridazine
Voriconazole

Table II. Selected antimicrobial medications reported to cause photo-induced drug eruptions

Subclass	Drug	Evidence
Tetracyclines	Tetracycline	–
	Doxycycline	PT[9] PP[9] RC[9]
	Minocycline	–
Nalidixic acid and the fluoroquinolones	Nalidixic acid	PT[10]
	Ciprofloxacin	PT[11]
	Sparfloxacin	PT[12]
	Ofloxacin	PT[13]
	Levofloxacin	–
	Moxifloxacin	–
Antituberculous	Isoniazid	PP[14] RC[14]
	Pyrazinamide	RC[15]
β-Lactams	Cefotaxime	PT[16]
	Ceftazidime	–
Miscellaneous antibiotics	Dapsone	PP[17] RC[18,19]
	Trimethoprim	RC[20]
Antifungals	Voriconazole	–
	Itraconazole	PT[21] RC[21]
	Ketoconazole	–
	Griseofulvin	–
Antimalarials	Quinidine	PP[22] PT[23] RC[23]
	Quinine	PP[24] PT[25]
	Hydroxychloroquine	PT[26] PP[26]
Antiretrovirals	Efavirenz	PT[27] PP[27,28]

PP = photopatch testing; **PT** = phototesting; **RC** = rechallenge; – indicates test not done or test negative.

cycline photosensitivity has been reported to manifest as photo-onycholysis,[80] pseudoporphyria[81] and solar urticaria.[82] Despite its prominent place among the known photosensitizing medications, our review of the literature did not find any phototesting, rechallenge or photopatch testing confirmation in reported cases of tetracycline photosensitivity.

The phototoxic reaction of doxycycline is dose dependent, as would be expected. Studies from Leeds, UK, demonstrated that phototoxicity occurs at doses of 100, 150 and 200 mg of doxycycline at rates of 3, 20 and 42%, respectively.[83,84] Eruptions reported include classic phototoxic eruptions, as well as onycholysis.[83-85] Phototesting with rechallenge testing and photopatch testing have been positive.[9]

2.1.2 Nalidixic Acid and the Fluoroquinolones

The antibiotic nalidixic acid and its derivatives, the fluoroquinolones, are known photosensitizers and are believed to cause both phototoxic and photoallergic eruptions.[10,86-88]

The clinical characteristics of photosensitivity reactions from ciprofloxacin are not well described in the literature, but one case of photo-induced purpura was reported.[89] *In vivo* testing has shown that ciprofloxacin lowers patients' MED, even if there is no clinical evidence of photosensitivity.[11] Photosensitivity to ciprofloxacin has been noted in patients with cystic fibrosis.[90,91]

Sparfloxacin is another fluoroquinolone that causes photosensitivity but was taken off the market because of other toxicities, particularly prolongation of the QT interval. A histopathological study of 13 patients revealed that sparfloxacin photosensitive eruptions have either a lichenoid or eczematous pattern on histology.[92] Photo-onycholysis has also been reported.[93] Interestingly, it has been shown that it is the combination of UVA and UVB together that cause sparfloxacin phototoxicity, rather than either alone.[12]

The two commonly used respiratory fluoroquinolones, levofloxacin and moxifloxacin, have very low phototoxic potential,[94-97] as does ofloxacin.[13,98]

Table III. Selected NSAIDs reported to cause photo-induced drug eruptions

Drug	Evidence
Naproxen	–
Ibuprofen	RC[29]
Celecoxib	–

RC = rechallenge; – indicates test not done or test negative.

Table IV. Antihypertensive medications reported to cause photoinduced drug eruptions

Subclass	Drug	Evidence
Diuretics	Thiazides	PP[30] PT[31]
	Furosemide	RC[32]
	Indapamide	–
	Triamterene	PP[33] RC[33]
ACE inhibitors	Ramipril	PP[34]
	Enalapril	–
	Quinapril	RC[35] PT[35]
Angiotensin receptor blockers	Valsartan	–
Calcium channel blockers	Amlodipine	PT[36]
	Nifedipine	RC[37]
	Diltiazem	PT[38] RC[39]
β-Blockers	Tilisolol	PP[40] RC[40]
Centrally acting agents	Rilmenidine	PT[41]
	Methyldopa	PP[42]

PP = photopatch testing; **PT** = phototesting; **RC** = rechallenge; – indicates test not done or test negative.

2.1.3 Other Antibiotics

Isoniazid and pyrazinamide, antibiotics used in the treatment of tuberculosis, have been implicated in causing photosensitive dermatoses. Isoniazid may cause a lichenoid eruption, and its photosensitizing effects have been confirmed by photopatch and rechallenge testing.[14] Pyrazinamide photosensitivity has been confirmed by rechallenge testing.[15]

Cefotaxime and ceftazidime, third-generation cephalosporins, have been implicated in PIDEs.[16,99] In the case of cefotaxime, photosensitivity manifested as photodistributed telangiectasia, while ceftazidime caused increased susceptibility to sunburn.

Dapsone is a sulfone antibiotic and anti-inflammatory agent that has been implicated in PIDEs, both phototoxic and photoallergic in nature.[17-19,100-102] Dapsone PIDE has been confirmed both by oral drug rechallenge and photopatch testing.[17-19] Trimethoprim, an antibiotic often used in combination with sulfamethoxazole, can also cause photosensitivity.[20]

2.1.4 Antifungals

Voriconazole is a triazole antifungal that has been reported to cause photosensitivity, usually with a classic phototoxic pattern and occasionally with cheilitis and pseudoporphyria.[103-108] In one series of five patients, the phototoxic reaction was initially misdiagnosed as chronic graft-versus-host disease.[109] The majority of the reports in the literature occur in patients receiving long-term prophylactic therapy with voriconazole for various immunocompromised states, particularly chronic granulomatous disease and solid-organ transplant recipients, and in many cases the photosensitive eruption appeared months after starting voriconazole therapy. While the acute photosensitive dermatitis usually resolves on discontinuation of voriconazole, there are multiple reports of subsequent significant photoaging as well as the development of squamous cell carcinoma and melanoma in the areas previously affected by the photosensitive eruption.[105,107,110-112] The increased risk of developing skin cancer in patients receiving a photosensitizing agent is also seen with oral psoralen, particularly 8-methoxypsoralen, in combination with UVA radiation. This treatment, known as PUVA, is used to treat a variety of skin diseases, including psoriasis. In the long-term follow-up studies of patients receiving PUVA, an increased risk of squamous cell carcinoma and melanoma has been documented, particularly in patients who have had over 200 treatments.[113,114] Psoralen is known to damage DNA and thus a long-term risk of phototoxicity may be an increased incidence of cutaneous malignancy.

Itraconazole, another triazole antifungal, has also been reported to cause photosensitivity in a predominantly phototoxic pattern with rechallenge evidence.[21] Fluconazole, however, has

Table V. Antiarrhythmic medications reported to cause photoinduced drug eruptions

Drug	Evidence
Amiodarone	PT[43,44]
Quinidine and quinine	See table II
Calcium channel blockers	See table IV

PT = phototesting.

Table VI. Psychotropic medications reported to cause photo-induced drug eruptions

Subclass	Drug	Evidence
Antipsychotics	Chlorpromazine	PP[45,46]
	Thioridazine	PP[47]
	Flupenthixol	Photoprick testing[48]
	Olanzapine	–
	Clozapine	–
Antidepressants	Imipramine	–
	Clomipramine	PP[49] RC[49]
	Escitalopram	–
	Paroxetine	PP[50,51]
	Fluoxetine	–
	Fluvoxamine	PP[51,52]
	Sertraline	–
	Citalopram	–
	Venlafaxine	PT[53]
	Phenelzine	–
Anxiolytics	Alprazolam	PT[54] RC[54]
	Chlordiazepoxide	RC[55]

PP = photopatch testing; **PT** = phototesting; **RC** = rechallenge; – indicates test not done or test negative.

not been reported to cause photosensitivity. Ketoconazole, an imidazole antifungal, can cause a phototoxic dermatitis.[115]

Griseofulvin is not thought to be a potent photosensitizer but has been reported in the literature.[116] UVA has been implicated and may interfere with porphyrin metabolism.

2.1.5 Antimalarials

Quinine causes a photosensitive dermatosis that has been described as having several different morphological appearances: oedematous, eczematous and lichenoid, with photo-onycholysis having also been described.[25,117-121] Photosensitivity from quinine may be persistent, which has been demonstrated experimentally and clinically.[25,118] In the 1987 study by Ferguson et al.,[25] two of two patients who underwent photochallenge testing had a positive reaction. While it has not been seen clinically, experimental data from photopatch testing suggest that quinine and quinidine may cross-react with regard to photosensitivity.[24]

Hydroxychloroquine is a rare cause of PIDEs, but it is a recognized entity and has been confirmed by photopatch testing.[26,122] Interestingly, hydroxychloroquine is used to treat polymorphous light eruption and systemic lupus erythematosus, two photosensitive conditions.

2.1.6 Antiretrovirals

Efavirenz is a non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV infection. Efavirenz-induced photosensitivity is very rare and has been reported three times.[27,28,123] While HIV infection and AIDS themselves may cause photosensitivity,[124] photopatch testing has provided evidence that efavirenz may be the culprit in some cases.[27,28]

2.2 NSAIDs

The NSAIDs are a heterogeneous group of medications that act by inhibiting prostaglandin synthesis. Photosensitivity has been reported most often with benoxaprofen, which has been withdrawn from the market, and piroxicam. Other implicated NSAIDs include nabumetone, ampiroxicam, tiaprofenic acid, naproxen, sulindac, meclofenamide sodium, oxaprozen and ibuprofen.[29,125-130] There are reports in the literature of photoallergic and pseudoporphyria reactions with the use of celecoxib, a cyclooxygenase 2 inhibitor.[131,132] Photopatch testing was carried out in one patient, but was negative.

Among the NSAIDs that are used most commonly, naproxen appears to have the most photosensitizing potential. Naproxen photosensitivity

Table VII. Cholesterol-lowering medications reported to cause photo-induced drug eruptions

Subclass	Drug	Evidence
HMG-CoA reductase inhibitors (statins)	Simvastatin	PT[56] PP[57] RC[57]
	Atorvastatin	PT[58] RC[58]
	Pravastatin	PT[56]
Fibrates	Fenofibrate	PT[59] PP[59] RC[59]

PP = photopatch testing; **PT** = phototesting; **RC** = rechallenge.

Table VIII. Chemotherapeutic medications reported to cause photo-induced drug eruptions

Drug	Evidence
Vandetanib	–
Imatinib	–
Paclitaxel	–
Hydroxyurea	–
Fluorouracil	–
Capecitabine	–
Tegafur	RC[60,61] PT[60] PP[62]
Flutamide	PP[63] RC[64]
Dacarbazine	RC[65]
Vinblastine	RC[66]
Epirubicin	PP[67]

PP = photopatch testing; **PT** = phototesting; **RC** = rechallenge; – indicates test not done or test negative.

usually presents as pseudoporphyria.[126,133] To our knowledge, there is only one report in the literature of ibuprofen-induced photosensitivity, which occurred in a phototoxic pattern.[29] Although the report did include rechallenge evidence, ibuprofen is generally not considered to be a potent photosensitizer.

2.3 Antihypertensives

2.3.1 Diuretics

The thiazide diuretics, including hydrochlorothiazide, have been reported to cause a variety of photosensitive eruptions, including an exaggerated sunburn reaction, dermatitis and a lichenoid eruption.[31,134] Chronic eczematous photosensitivity lasting months to years after discontinuation of the drug has been reported.[135] A group of patients with chronic photosensitivity was treated successfully with PUVA.[135] A study by Addo et al.[31] determined that thiazide photosensitivity can be elicited by wavelengths in both the UVA and UVB range. Positive photopatch testing to hydrochlorothiazide has been reported.[30]

Bullous photoeruptions have been reported secondary to treatment with furosemide, particularly in very high doses.[32,136] Rechallenge testing has been positive.[32] Indapamide has been reported to cause photo-onycholysis, but this drug was not found to cause a decreased MED on phototesting and did not cause a positive photopatch test result.[137] Clinical photosensitivity to triamterene, a potassium-sparing diuretic, is rare. A single patient was rechallenged with triamterene, with photopatch testing confirmation.[33]

2.3.2 ACE Inhibitors and Angiotensin Receptor Blockers

The ACE inhibitors and angiotensin receptor blockers (ARBs) are two groups of antihypertensive medications that work on the renin-angiotensin-aldosterone pathway. They have become mainstays of antihypertensive treatment for patients with diabetes, renal failure and heart failure. Among the ACE inhibitors, ramipril, quinapril and enalapril have been reported to cause photosensitivity, with positive photopatch testing results for ramipril and rechallenge evidence for quinapril.[34,35,138] There is one report in the literature of valsartan-induced photosensitivity.[139] To our knowledge, it is

Table IX. Miscellaneous medications reported to cause photo-induced drug eruptions

Class	Drug	Evidence
Retinoids	Etretinate	PT[68] PP[69] RC[69]
	Isotretinoin	–
Contraceptive hormones	Ethinylestradiol	RC[70,71]
Antihistamines	Ranitidine	RC[72]
	Diphenhydramine	PP[73]
	Mequitazine	PP[74]
	Repirinast	PT[75] RC[75]
Anticonvulsants	Carbamazepine	PP[76] RC[76]
Oral hypoglycaemic agents	Glibenclamide (glyburide)	PT[77]
Antiplatelet agent	Clopidogrel	RC[78]
Monoclonal antibody	Eculizumab	–
Anti-inflammatory	Leflunomide	–
	Mesalazine	–

PP = photopatch testing; **PT** = phototesting; **RC** = rechallenge; – indicates test not done or test negative.

the only ARB that has been reported to cause photosensitivity.

2.3.3 Calcium Channel Blockers

Amlodipine and nifedipine are calcium channel blockers (CCBs) in the dihydropyridine group that have been reported to cause photodistributed facial telangiectasia, a distinct photoinduced morphology, and may in fact cross-react with each other with regard to this phenomenon.[36,140,141] Nifedipine has also been reported to cause a photodermatitis, confirmed by rechallenge.[37] However, photopatch testing, carried out on one of two patients, was negative.

Diltiazem, a benzothiazepine CCB, has been implicated as a cause of photodistributed hyperpigmentation.[38,142] It has also been reported to cause photosensitivity dermatitis, proven by rechallenge.[39]

2.3.4 Others

The β-blocker tilisolol has been reported to cause photosensitivity in a single patient with confirmation by rechallenge and photopatch testing.[40] Rilmenidine, a central imidazoline agonist, has been reported to cause erythema and swelling in a photodistributed pattern, again in one patient.[41] Methyldopa, another centrally acting antihypertensive, may cause photosensitivity, and this has been demonstrated with positive photopatch testing in one patient.[42]

2.4 Antiarrhythmic Medications

2.4.1 Amiodarone

Amiodarone is perhaps the best studied of all photosensitizing medications. In some reports, photosensitive eruptions were seen in over 50% of patients taking amiodarone,[143-145] but a more recent study found it to occur in only 7 of 98 patients.[146]

Amiodarone photosensitivity classically presents as a burning and tingling sensation in sun-exposed skin with associated erythema. Particularly after long-term exposure, amiodarone induces a distinctive blue-grey pigmentation on sun-exposed sites in 1–2% of patients.[43,143] The photosensitivity usually resolves within months of discontinuation of the drug; however, it has been reported to be persistent.[147] Photo-induced pigmentation generally fades gradually over 1–2 years.[148] UVA and UVB are both involved in amiodarone-induced photosensitivity.[43,44]

Quinidine photosensitivity has been reported, and can present as an eczematous dermatitis, a lichenoid eruption or a livedoid purpuric eruption.[23,149,150] In one report, the histology and clinical presentation were consistent with a photoallergic reaction.[150] The diagnosis was confirmed in one study by phototesting and rechallenge, and in another by photopatch testing.[22,23]

Other antiarrhythmics that cause photosensitivity, the calcium channel blockers and quinine, are discussed in earlier sections of this paper.

2.5 Psychotropic Medications

2.5.1 Antipsychotics

The phenothiazine antipsychotics, chlorpromazine and thioridazine, have both been reported to cause photosensitivity, with thioridazine photosensitivity thought to be less common.[47,151] Patients taking chlorpromazine may experience an exaggerated sunburn reaction, and lichenoid and bullous eruptions have also been reported.[45,46,152] Patients taking both thioridazine and chlorpromazine have had positive photopatch responses to the implicated drugs.[45-47] Long-term, high-dose therapy with either chlorpromazine or thioridazine can result in photodistributed slate-grey to violaceous hyperpigmentation.[151] Flupenthixol, an antipsychotic drug structurally related to the phenothiazines, has also been reported to cause photosensitivity.[48] Parenterally administered antipsychotics have also been reported to cause a photocontact dermatitis in nurses administering the medications.[153,154]

The atypical antipsychotic olanzapine has been reported to cause photo-onycholysis, but is generally not thought of as a potent photosensitizing medication.[155] Photosensitivity to clozapine has also been reported.[156]

2.5.2 Antidepressants

The tricyclic antidepressants are chemically related to the phenothiazines and have also been reported to cause photosensitivity. Imipramine may cause photodistributed erythema, and after

long-term exposure may cause slate-grey hyperpigmentation.[157,158] Clomipramine has been implicated as a cause of photoallergy, with photopatch and rechallenge testing having been performed.[49]

Selective serotonin reuptake inhibitors (SSRIs) are now the most commonly prescribed antidepressant medications. While they are not considered potent photosensitizers, a number of them have been reported to cause PIDEs. In their report of erythroderma on sun-exposed sites following artificial tanning while taking ecitalopram, Ram-Wolf et al.[159] reviewed all of the reported cases of SSRI photosensitivity in the literature to that point. Paroxetine,[50,51] and fluvoxamine[51,52] have both demonstrated photosensitivity with photopatch positivity. Fluoxetine may cause erythema and blisters,[160] sertraline may cause macular erythema[161] and citalopram may cause photodistributed hyperpigmentation.[162]

Venlafaxine, a serotonin-noradrenaline (norepinephrine) reuptake inhibitor (SNRI), has been reported to cause photodistributed telangiectasia.[53] As yet there are no reports of duloxetine, another SNRI, causing photosensitivity. The monoamine oxidase inhibitor phenelzine has been reported to cause clinical photosensitivity.[163]

2.5.3 Anxiolytics

Alprazolam, a benzodiazepine anxiolytic, has been reported to cause pruritic erythema in sun-exposed sites, with photosensitivity confirmed by rechallenge.[54,164] Chlordiazepoxide has also been implicated as a cause of a photo-induced eczematous eruption.[55]

2.6 Cholesterol-Lowering Agents

The HMG-CoA reductase inhibitors (statins), medications commonly used to lower cholesterol, have been rarely reported to cause photosensitivity. Simvastatin may cause a persistent photodistributed dermatitis.[57,165] Photopatch testing and rechallenge with phototesting have both been positive.[57] Atorvastatin has been reported to cause an oedematous erythema on sun-exposed sites, proven by rechallenge.[58] Both simvastatin and pravastatin have been reported to cause photodistributed erythema multiforme.[56]

Fenofibrate is another lipid-lowering agent that works by a distinct mechanism. It has been reported to cause eczematous and lichenoid photosensitivity, proven by both photopatch testing and rechallenge.[59,166,167]

2.7 Chemotherapeutic Agents

The drugs detailed in this section are very diverse structurally and in their mechanism of action, although they all have antineoplastic applications.

Vandetanib, a tyrosine kinase inhibitor, caused a photodistributed erythematous and bullous eruption in a patient being treated for hepatocellular carcinoma.[168] Imatinib, another drug in this class, has been reported to cause exaggerated sunburn reactions in patients being treated for chronic myelogenous leukaemia.[169]

Fluorouracil and a number of related compounds have been reported to cause photosensitive eruptions. Fluorouracil can cause enhanced sunburn reactions, photodistributed hyperpigmentation or polymorphous light eruption-like syndromes.[170] Tegafur, a fluorouracil derivative, may cause both lichenoid and eczematous photodistributed eruptions.[60,62] Rechallenge, as well as photopatch testing, have been positive, with photopatch testing being positive in only those cases where the reaction was eczematous.[61,62] Capecitabine, a fluorouracil pro-drug, may cause a photodistributed lichenoid eruption.[171,172] It may be considered less photosensitizing than fluorouracil and may be an alternative treatment for those patients unable to tolerate fluorouracil secondary to photosensitivity.[173]

Paclitaxel has been reported to cause photodistributed erythema multiforme as well as onycholysis.[174,175] Hydroxyurea may cause a photodistributed granulomatous reaction.[176] Photosensitive eruptions to dacarbazine have been reported and rechallenge evidence exists.[65,177,178] Additionally, there is rechallenge evidence for vinblastine phototoxicity in a patient who developed a photodistributed vesicular eruption while on the drug.[66] Photopatch testing

was positive in a patient with a bullous eruption secondary to epirubicin.[67]

Flutamide, used commonly for prostate cancer, has been reported to cause photosensitivity a number of times, with documented photopatch and rechallenge positivity.[63,64,179]

Methotrexate is often listed as a photosensitizing medication in review articles and other publications.[8] However, methotrexate is not, in fact, a photosensitizing drug, but rather produces what are called radiation recall phenomena, i.e. areas where patients have had sunburns in the past may erupt again upon exposure to methotrexate.[180-182]

2.8 Miscellaneous Medications

Systemic retinoid medications have often been implicated as causes of photosensitivity, but this is controversial. The 1989 article by Ferguson and Johnson[68] addressed this controversy with a literature review and experimental testing with etretinate and isotretinoin. They found both clinical and experimental evidence of etretinate photosensitivity but failed to find clinical or experimental evidence of isotretinoin photosensitivity. A similar study found no clinical evidence of isotretinoin photosensitivity and minimal experimental evidence, which the authors did not think was significant.[183] Etretinate-induced photosensitivity typically manifests as increased susceptibility to sunburn. Etretinate has also been reported to cause photoleukomelanoderma.[69]

Hormone contraceptives have been implicated as rare causes of photosensitivity. A recent report found a contraceptive patch containing norelgestromin and ethinylestradiol to be photosensitizing, with recurrence of the erythematous, vesicular eruption when the patient was switched to an oral contraceptive pill (OCP) containing ethinylestradiol and drospirenone. The report concluded that ethinylestradiol was most likely the offending agent. Rechallenge phototesting with the OCP was positive.[70] Another case report described a patient with photosensitivity to an OCP containing ethinylestradiol and desogestrel, with recurrence of the eruption on rechallenge, with a second pill containing ethinylestradiol and levonorgestrel.[71] It can therefore be concluded that photosensitivity to ethinylestradiol is a rare but real entity.

Ranitidine, an antihistamine used to treat gastroesophageal reflux disease, has been reported to cause a papulosquamous eruption on sun-exposed sites confirmed by rechallenge.[72] Diphenhydramine, another antihistamine, has caused photosensitivity, with photopatch test positivity.[73] The phenothiazine antihistamine mequitazine has been demonstrated to be photosensitizing, with positive photopatch testing results.[74] Repirinast has been reported to cause solar urticaria.[75]

Carbamazepine has been reported to cause a photosensitive lichenoid eruption, with photopatch and rechallenge evidence.[76] Glibenclamide (glyburide), a sulfonylurea oral hypoglycaemic agent, has been reported to cause an eczematous photodermatitis.[77] While phototesting has revealed increased sensitivity to UVA and UVB with glibenclamide, photopatch testing has been negative and rechallenge testing has not been performed.[77] Clopidogrel, an antiplatelet agent, has been reported to cause a lichenoid photodistributed eruption, confirmed by rechallenge.[78]

Eculizumab, leflunomide and mesalazine have all been reported to cause photosensitivity, but none, to the best of our knowledge, have been evaluated by phototesting or photopatch testing.[184-186]

3. Prevention and Management

The first step in managing a patient with a PIDE is to make a diagnosis of photosensitivity and then to determine if there is a possible culprit drug. This is accomplished by physical examination, with a photodistributed pattern to the eruption, and is accompanied by thorough history taking, particularly the chronology of medication in relation to the onset of the cutaneous eruption. Diagnostic tests, including phototesting, photopatch testing, clinical rechallenge and rechallenge phototesting, as described in section 1, may be carried out. Once a diagnosis of a drug-induced photosensitivity disorder is made and the offending drug has been identified, the most important aspect of management is discontinuation

of the drug.[3] While persistent photosensitivity may occur, in most cases the photosensitivity will abate shortly after the photosensitizing medication is discontinued.

Other measures that may be helpful in the treatment of a photosensitive eruption include the use of topical or systemic corticosteroids, depending on the severity of the eruption. One study regarding sparfloxacin photosensitivity found that delayed treatment of photosensitive eruptions may make them more difficult to treat. As such, treatment of the eruption as early as possible is advisable.[92]

Discontinuation of a drug may not be possible for all patients. In such cases, secondary preventive measures such as avoidance of exposure to sunlight and the use of protective clothing and broad-spectrum sunscreens with protection against both UVA and UVB should be implemented.

Another strategy that has been reported to work in the secondary prevention of PIDEs is the administration of medications in the evening rather than during the daytime.[187] Of course, the appropriateness of this strategy must be assessed on a drug-by-drug basis, taking into account its pharmacokinetic properties.

One patient with amiodarone-induced photosensitivity was treated with gradually increasing doses of narrow-band UVB phototherapy in an attempt to induce improved tolerance to sun exposure. This treatment is more often used to treat patients with polymorphous light eruption, a photosensitivity disorder that may be immune mediated. The patient had been found to be sensitive to UVA and visible radiation and the narrow-band UVB phototherapy allowed the patient to increase symptom-free time outdoors, increasing the tolerated time from <30 minutes to 3–4 hours.[188]

With regard to primary prevention of PIDEs, physicians should counsel patients about sun avoidance and protection when they initiate treatment with a known photosensitizing medication. While all of the medications listed in tables II–IX may cause photosensitivity, counselling about this potential side effect may not be necessary for all of these medications. Rather, only those medications that are considered potent photosensitizers, as listed in table I, warrant physician and patient awareness prior to their prescription.

4. Conclusions

While the exact incidence of drug-induced photosensitivity is unknown, both in general and for individual drugs, it is clearly an important clinical entity. The diagnosis of PIDEs is largely clinical, but can be aided by diagnostic tools such as phototesting, photopatch testing and rechallenge testing. A large number of medications have been implicated in the literature as causes of PIDEs, many with convincing clinical and scientific support. However, in our opinion, there are only ten medications, as listed in table I, that should be thought of as potent photosensitizers.

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