Phototoxic Dermatitis

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Contents

Abstract

Phototoxicity is more frequent than photoallergy, but it is not always easy to distinguish between these two patterns of photosensitivity.

Phytophotodermatitis from plants containing furocoumarins is one of the main causes of phototoxic contact dermatitis.

Topical and systemic drugs are a frequent cause of photosensitivity, often with phototoxic aspects.

The main clinical pattern of acute phototoxicity is an exaggerated sunburn, but bullae, purpura, pseudoporphyria, photoonycholysis, and dyschromia can also occur.

Exposure to phototoxic drugs is increasingly associated with enhanced skin carcinogenesis.

Keywords

Photosensitivity · Phototoxicity · Photoallergy · Drug photosensitivity · Phytophotodermatitis

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1 Core Messages

- Phototoxic dermatitis from exogenous chemicals can be polymorphic.
- It is not always easy to distinguish phototoxicity from photoallergy.
- Phytophotodermatitis from plants containing furocoumarins is one of the main causes of phototoxic contact dermatitis.
- Topical and particularly systemic drugs are a frequent cause of photosensitivity, often with phototoxic aspects.
- The main clinical pattern of acute phototoxicity is an exaggerated sunburn.
- Subacute phototoxicity from systemic drugs can present as pseudoporphyria, photoonycholysis, and dyschromia.
- Long term exposure to phototoxic drugs can enhance skin carcinogenesis.

2 Introduction

Phototoxicity is included within the spectrum of photosensitive disorders and represents an abnormal skin reaction to the sun or other sources of light, mostly ultraviolet light (UV). It is due to the presence of an abnormal chromophore in the skin, either an endogenous or exogenous chemical that is selectively activated by solar radiation and will ultimately induces aggression of skin cells and inflammation (Ferguson 1999; Gonçalo 2011). A state with reduced skin defense against UV aggression (vitiligo, low niacin levels, xeroderma pigmentosum) may potentiate the acute reaction and lower the thresholds for the acute inflammation or the effects of chronic phototoxicity (Gonçalo and Giménez-Arnau 2015; Khandpur et al. 2017).

Phototoxicity does not involve a specific T-cell-dependent response to the chromophore. This is the hallmark of photoallergy. Nevertheless, phototoxicity generates an innate immune response with significant danger signals that may promote the presentation of the chemical or one of its photoproducts to the immune system, therefore favoring T-cell sensitization and photoallergy. Both patterns of photosensitivity (phototoxicity and photoallergy) may coexist, and it is sometimes difficult to distinguish the contribution of each of these pathomechanisms in each case of photosensitivity.

Awareness of photosensitivity is increasing due to the new patterns of life with increased exposure to natural or artificial light (Elkeeb et al. 2012) and the more frequent exposure to chemicals with photosensitizing properties (drugs, UV filters and cosmetics), but more attention is also taken on the pre-marketing studies to evaluate the photosensitizing potential of chemicals (Kim et al. 2015; Onoue et al. 2017).

Phototoxicity is mostly related with acute or chronic exposure to topical or systemic exogenous chemicals (plants and drugs). It is probably frequent and certainly underreported as it may present as minor symptoms (skin prickling/burning or erythematous sunburn) that resolve with no medical intervention or it may occur under clinical patterns that may not immediately be recognized as exogenous photosensitivity (lichenoid reactions, telangiectasia, lupus erythematosus, actinic keratosis, and skin cancers) (Sontheimer et al. 2008; Gonçalo 2011; Dawe and Ibbotson 2014; Khandpur et al. 2017).

3 General Mechanisms of Phototoxicity from Exogenous Chemicals

The skin has natural chromophores (aminoacids, DNA bases, melanin, porphyrins, etc.) in order to be prepared to live under the sun and benefit from sunlight, namely, with the activation of 7-dehydrocholesterol by UVB to form pro-vitamin D3, subsequently converted into Vitamin D. But there are also harmful effects of the activation of cutaneous biologic systems by sunlight, namely, photoaging and photocarcinogenesis.

Photosensitivity develops when the concentration of a natural chromophore is higher than normal or when an abnormal chromophore, endogenous or mostly exogenous, is present in the skin that is simultaneously exposed to light.

The chromophores involved in cutaneous photosensitivity are chemicals, usually with double

bonds or halogenated aromatic rings (Mang et al. 2011) that can be selectively activated by photons with a particular wavelength, particularly UVA (320–400 nm), seldom UVB (290–320 nm), or visible light. Even though some chromophores absorb in the UVB which is more energetic, UVA penetrates the skin more deeply and, particularly for systemic chromophores, this is certainly the most important spectrum for inducing photosensitivity (Elkeeb et al. 2012). Only exceptional cases have a well-documented exogenous photosensitivity exclusively from UVB (Fujimoto et al. 2009; Elkeeb et al. 2012).

The molecular processes conducting to phototoxicity are complex, and each chromophore may induce particular mechanisms conducting to photosensitivity. In general, the electrons in the outer orbits receive the energy of the UV photons and the molecule becomes excited. The chemical can then undergo several types of modifications within itself (isomerization, breaking of double bounds, oxidation) or react with neighboring molecules, in the presence of absence or oxygen, eventually forming free radicals or reactive oxygen species (ROS). If the cellular repair mechanisms do not act immediately (antioxidant systems, endonucleases for DNA repair), there is modification of unsaturated lipids of cell membranes, aromatic amino acids of proteins, and pyrimidine bases of DNA or RNA causing cellular lesion or death. The activation of intracellular signaling pathways (NF-κB, MAP-kinases, the Nrf-2 antioxidant response element pathway, and the inflammasome) generates soluble inflammatory mediators (prostaglandins, leukotriene, interleukins (IL)-1, 6, 8, other cytokines and chemokines) with consequent inflammation and skin lesions (Hawk 1999; Ferguson 1999; Mang et al. 2011). In photoallergy, the energy of the photon transforms the chromophore into a stable photoproduct or enhances its reaction with an endogenous peptide forming a hapten or an allergen. This is captured by skin antigen-presenting cells and sensitizes T cells, that in a further exposure to the same chemical will generate a specific T-cell immune reaction – adaptive immunity/type IV hypersensitivity reaction (Mang et al. 2011; Peiser et al. 2012; Elkeeb et al. 2012).

Several phototoxic substances, like psoralens, chlorpromazine, some nonsteroidal anti-inflammatory drugs and fluorquinolones, apart from the capacity to generate free radicals and cell death responsible for acute phototoxicity, also enhance chromosomal damage in the presence of UV, both in vitro and in vivo (Seto et al. 2010). They are photo-genotoxic and photomutagenic and usually also enhance photoimmunosupression, with consequent implications in photocarcinogenesis (Müller et al. 1998; Klecak et al. 1997; Marrot et al. 2003; Lhiaubet-Vallet et al. 2009; Palumbo et al. 2016). Epidemiological studies and several clinical reports also show enhancement of photocarcinogenesis in humans exposed to photoactive chemicals (Placzek et al. 1999; Karagas et al. 2007; Jensen et al. 2008; Cowen et al. 2010; Miller et al. 2010; Siiskonen et al. 2013; Dawe and Ibbotson 2014).

3.1 Phototoxicity Versus Photoallergy

Photosensitivity from exogenous chemicals is mainly caused by phototoxicity, but many of these phototoxic chemicals can also induce photoallergy in susceptible individuals, and sometimes both mechanisms may coexist and overlap (Dawe and Ibbotson 2014; Gonçalo and Giménez-Arnau 2015).

Classically, phototoxicity is more frequent and develops in every individual, as long as enough photosensitizer and sun exposure are simultaneously present. It is dependent on the dose of UV and the photosensitizing chemical. The reaction can occur on a first and single contact, with no flare-ups or cross-reactions in further exposures, appears mainly as a sharply demarcated erythema exclusively on sun-exposed areas (mimicking sunburn), resolves with hyperpigmentation and, on histology, apoptotic keratinocytes (sunburn cells) are abundant.

On the other extreme, photoallergy develops only in a limited number of individuals and needs previous sensitization but can develop also with cross-reactive chemicals. It is not dose-dependent, can occur even with low UV exposure, and

appears mostly as eczema that can spread to non-UV-exposed sites and, on skin biopsy, there is mainly T-cell infiltration, spongiosis, and vesicles (Table 1).

These are the typical aspects of the polar aspects of photosensitivity, but it is not always possible to distinguish them based on the clinical aspects, histopathology or photopatch or photoprovocation test results, or even by the culprit chemical.

Except for a few chemicals with no intrinsic phototoxic potential that give rise to stable photoproducts, like piroxicam and olaquindox, and induce only photoallergy (Figueiredo 1994), most substances can induce both phototoxic and photoallergic reactions. Actually some individuals develop photoallergy from highly phototoxic chemicals like psoralens (Ljunggren 1977; Möller 1990; Karimian-Teherani et al. 2008; Bonamonte et al. 2010), phenothiazines (Kerr et al. 2008b; Cardoso et al. 2009), or fluorquinolones (Kurumajin and Shono 1992; Gonçalo 1998; Oliveira et al. 1996). Very probably, as for contact allergens that have an inherent "irritant" potential that awakens the innate immune system and promotes sensitization (Neves et al. 2008), most photoallergens also have some phototoxic potential. This innate inflammatory reaction can be the "danger signal" necessary to initiate sensitization.

Table 1 Distinction between acute phototoxicity and photoallergy

	Phototoxicity	Photoallergy
Frequency	High	Low
Latency period/ sensitization	No	Yes
Doses of UV/photosensitizer	High	Low
Cross-reactions	No	Yes
Morphology of lesions	Sunburn, polymorphic	Eczema, erythema multiforme
Sharp limits	Yes	No
Covered areas	Not involved	Possibly involved
Resolution	Quick	May recur, persistent reactors
Residual hyperpigmentation	Yes	No
Histology	Sunburn cells	Eczema
Pathomechanism	DNA/cell damage ROS/inflammation	Type IV hypersensitivity photoproduct
Photopatch tests	Not indicated Nonspecific positive reaction	Positive, particularly in photoallergic contact dermatitis

Photosensitivity developing on the first exposure to the chemical is typical of phototoxicity, whereas photoallergy needs several exposures to induce sensitization before lesions develop. Nevertheless, in an enigmatic way, photoallergy to piroxicam and ketoprofen occurs often at the first exposure. This is explained as individuals are previously sensitized or photosensitized to a molecule similar to their photoproducts, namely the contact allergen thimerosal and its moiety thiosalicylic acid, in the case of piroxicam (Gonçalo et al. 1992; Ikezawa et al. 1992; Hariva et al. 1993; Figueiredo 1994) or cinnamic alcohol or a benzophenone, in the case of ketoprofen (Foti et al. 2008; Avenel-Audrun et al. 2010; Stingeni et al. 2010).

Phototoxicity is considered to occur in every patient as long as enough chromophore and sun are present at the same time, but there is some individual susceptibility that is not completely understood. In systemic drug photosensitivity, we may suspect that differences in drug metabolism may generate different amounts of the photoactive metabolite and thickness of the horny layer or the degree of melanin pigmentation may influence both systemic drug phototoxicity, phytophotodermatitis, or contact phototoxicity (Zaheer et al. 2016), but other susceptibility factors for developing phototoxicity need further investigation.

Acute phototoxicity presents mainly as an exaggerated sunburn reaction, but it may develop vesicles and bullae that may be difficult to distinguish from photoallergy. Hyperpigmentation, typical of phototoxicity, may also develop as a consequence of photoallergy, as in cases induced by fragrances (Gonçalo et al. 1991).

Photoallergic reactions may recur and become persistent and eventually progress to chronic actinic dermatitis with extreme photosensitivity in the absence of exposure to the culprit chemical (Hawk 2004; Béani 2009), whereas phototoxic reactions

are considered transient. Nevertheless it is important to be aware that phototoxic reactions or even subclinical phototoxicity may induce long-term damage (photoaging and photocarcinogenesis).

4 Clinical Patterns of Phototoxicity from Exogenous Chemicals

Photosensitivity from exogenous chemicals can present under various clinical patterns with acute and delayed lesions: urticaria, eczema or erythema multiforme-like lesions (mainly in acute photoallergy), erythema, edema and bullae with progression to hypo or hyperpigmentation (mainly in acute phototoxicity), or as lichenoid reactions, subacute or chronic cutaneous lupus erythematosus, photoaging and actinic keratosis, and squamous cell carcinomas (late reactions).

Lesions can be very evocative of phototoxicity, as in phytophotodermatitis, acute exaggerated sunburn, or photoonycholysis, but sometimes the diagnosis or even the suspicion of photosensitivity is not so obvious (cutaneous lupus erythematosus or telangiectasia) particularly when there is no immediate or evident relation with exposure to the sun and the exogenous chemical (actinic keratosis and skin cancer) (Table 2).

Skin lesions can occur immediately after sun exposure (photocontact urticaria), within 12–24 hours or a few days (acute phototoxic or photo-allergic reactions), several days or weeks (pseudoporphyria, photo-onycholysis or subacute lupus erythematosus), or months or years (drug-enhanced photoaging and photocarcinogenesis).

Table 2 Clinical patterns of photosensitivity

Predominant in phototoxicity	Predominant in photoallergy
Exaggerated "sunburn"	Urticaria in sun-exposed area
Pseudoporphyria	Acute or subacute eczema
Photoonycholysis	Erythema multiform-like
Hyperpigmentation/ hypopigmentation (vitiligo-like lesions)	Lichenoid reactions
Telangiectasia and/or Purpura	Subacute or chronic lupus erythematosus
Pellagra-like reactions	
Actinic keratosis and squamous cell carcinoma	

Localization of the lesions depends on whether the photoactive chemical is directly applied on the skin (photocontact dermatitis) or the photosensitizer reaches the skin after systemic exposure.

In photosensitivity from a topical agent, dermatitis draws the area of application and concomitant sun exposure, but distant lesions can occur in areas of accidental contact, as in a contralateral limb (kissing faces of the legs), and in areas of inadvertent spread by the hands or contaminated objects (Hindsén et al. 2004; Lasa Elgezua et al. 2004). Connubial/consort dermatitis can also occur from contact photosensitizers (Fernández-Jorge et al. 2008). Some topical nonsteroidal anti-inflammatory drugs (NSAIDs) are considerably absorbed through the skin and lesional distribution can mimic systemic photosensitivity.

In systemic photosensitivity, the reaction usually involves, in a symmetric distribution, UV-exposed areas of the face, the V-shaped area of the neck and upper chest, dorsum of the hands and forearms, and occasionally also the legs and dorsum of the feet. UV-shaded areas of the face and neck are spared like the upper eyelids, upper lip, deep facial wrinkles (Fig. 1), retroauricular areas, a submandibular rhomboid area, and areas covered by the beard, hair, or clothing. In systemic photosensitivity or after using oral solutions, the lower lip can be mainly or almost exclusively involved, because of its higher UV exposure and, very probably, because of the thinner corneal layer more prone to phototoxic reactions (Auffret et al. 2006; Cardoso et al. 2009; Canelas et al. 2010).

Large body folds, like the axillae, groins, finger webs, and areas covered by clothing or other accessories (watch strip, shoes) (Fig. 2), are also usually spared. Involvement of these shaded areas suggests dermatitis from an airborne allergen or irritant.

Asymmetric sun exposure, as in car drivers who only expose the left arm, or limited exposure to artificial light can change localizations accordingly.

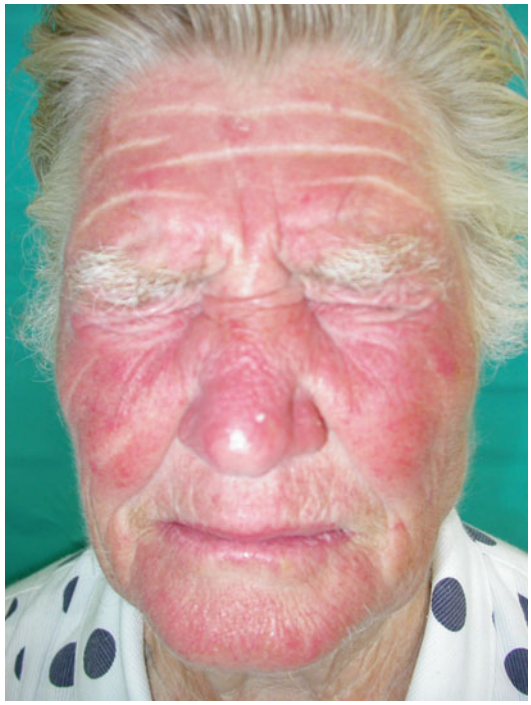

Fig. 1 Acute phototoxicity from amiodarone, mimicking sunburn, and sparing the deep facial wrinkles

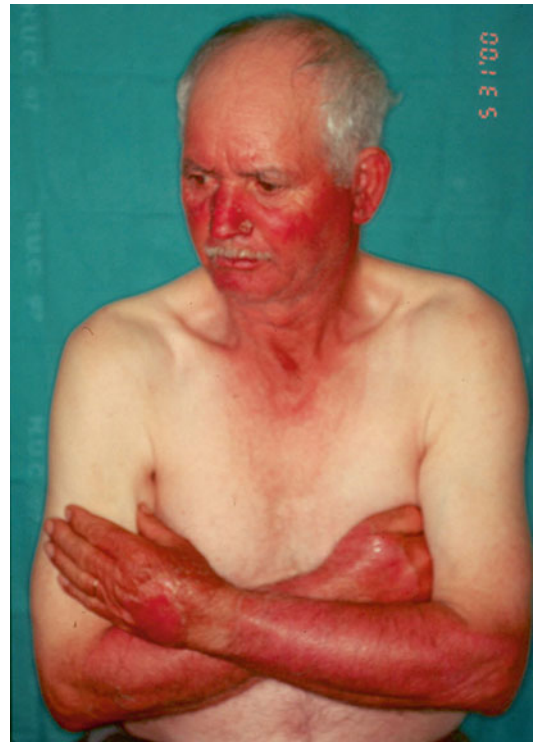

Fig. 2 Photosensitivity from systemic lomefloxacin, sparing the sunshaded areas of the trunk, arm, and front covered by clothing and hat and also the wrist protected from the watch

4.1 Acute Patterns of Phototoxicity

4.1.1 Immediate Reactions

Immune-mediated or nonimmune urticaria as a manifestation of photosensitivity from an exogenous chemical has been described with 5-aminolevulinic acid used in photodynamic therapy (Kerr et al. 2007), oxybenzone in sunscreens (Collins and Ferguson 1994), and chlorpromazine (Lovell et al. 1986). Some drugs, like amiodarone, benoxaprofen (removed from the market), and vemurafenib, induce immediate prickling and burning with transient erythema as a manifestation of photosensitivity (Ferguson 1999; Dummer et al. 2012; Gelot et al. 2013; Brugière et al. 2014).

4.1.2 Acute Phototoxic Dermatitis, Mimicking Sunburn

The main clinical pattern of acute phototoxicity (exaggerated sunburn) develops within 12–24 h of sun exposure with a sharply demarcated erythema with prickling and burning, eventually with skin pain but typically without pruritus. Erythema can progress to vesicles and bullae, but eczematous lesions with small vesicles or multiforme-like lesions are not usual. Photo-induced Stevens-Johnson syndrome/toxic epidermal necrolysis has also been associated with drug phototoxicity (Redondo et al. 1996; Moghaddam and Connolly 2014).

Like in exaggerated sunburn, large sheets of necrotic epidermis will detach within the next days and hyperpigmentation may occur (Fig. 2).

4.2 Subacute Patterns of Phototoxicity

Some clinical patterns of phototoxicity develop within days or weeks after exposure to the photosensitizer and the sun: pseudoporphyria, photoonycholysis, hyper- or hypopigmentation, telangiectasia, and purpura.

4.2.1 Pseudoporphyria

Pseudoporphyria presents as chronic skin fragility with flaccid bullae and easy bruising on non-inflamed exposed skin, which resolve completely or occasionally, with milia formation. It resembles porphyria cutanea tarda both clinically and on histopathology (bullae formation below the lamina densa and a poor dermal inflammatory infiltrate). It occurs in individuals with no inborn error of porphyrin metabolism and no increase of endogenous porphyrins (Glatz and Hofbauer 2012; Dawe and Ibbotson 2014; Gonçalo and Giménez-Arnau 2015; Gonçalo 2016).

Pseudoporphyria was initially described in individuals exposed to phototoxic drugs like nalidixic acid, furosemide, tetracyclines and naproxen, predominantly in children (Ferguson 1999; Gonçalo and Giménez-Arnau 2015; Rok et al. 2015). More recently others drugs have been associated with this phototoxic reaction pattern: ciprofloxacin (Schmutz et al. 2008), celecoxib (Cummins et al. 2000) (Schmutz et al. 2006), voriconazole (Auffret et al. 2006; Tolland et al. 2007; Hickman et al. 2010; Riahi and Cohen 2011), torsemide (Pérez-Bustillo et al. 2008; Quaiser et al. 2015), imatinib (Timmer-de Mik et al. 2009; Berghoff and English 2010), finasteride (Santo Domingo et al. 2011), and metformin (Lenfestey et al. 2012), and in Australia, it has been associated with detoxifying drinks rich in chlorophyll (Zhao et al. 2016).

Pseudoporphyria represents a typical phototoxic reaction where the drug, as the uroporphyrin in the hereditary disease, induces phototoxicity probably through singlet oxygen (Ferguson 1999; Figueiredo 1994).

4.2.2 Photoonycholysis

Photoonycholysis is a typical pattern of phototoxicity, occurring most often as the single manifestation (Fig. 3). It presents most often as a half-moon distal onycholysis of one or several nails, but it can occur as a circular notch in a single finger, a yellow staining of the nail bed or a bullae under the nails (Baran and Juhlin 2002). It appears late (2–3 weeks after drug intake and sun exposure), sometimes preceded by pain in the nail apparatus.

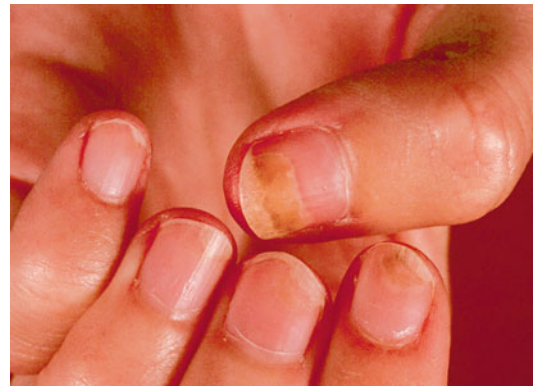

Fig. 3 Photoonycholysis from chlortetracycline

Photoonycholysis occurs mainly with tetracyclines (demeclocycline, doxycycline) (Passier et al. 2004; Goetze et al. 2017), psoralens, NSAIDs (diclofenac), and fluorquinolones (Baran and Juhlin 2002; Glatz and Hofbauer 2012; Al-Kathiri and Al-Asmaili 2016). There is no definite explanation for the isolated nail involvement: the nail bed is relatively unprotected from sunlight with fewer melanocytes and the nail plate may work as a lens focusing the energy to cause the inflammatory reaction and induce detachment of the nail plate from the nail bed (Baran and Juhlin 2002; Passier et al. 2004; Gregoriou et al. 2008; Al-Kathiri and Al-Asmaili 2016).

4.2.3 Dyschromia

Hyperpigmentation following an acute phototoxic reaction is similar to the normal UV response with IL-1alfastimulating keratinocytes to produce melanotropins and activate melanocytic pigmentation (Rok et al. 2015; Khandpur et al. 2017). This hyperpigmentation occurs typically with psoralens, namely in phytophotodermatitis (Fig. 3).

Hypopigmentation has been described in flutamide-induced photosensitivity (vitiliginous lesions with sharp limits after the acute reaction) (Vilaplana et al. 1990; Gonçalo et al. 1999), and photoleukomelanoderma has been observed after chronic exposure to hydrochlorothiazide (Khandpur et al. 2017).

Dyschromia from the dermal accumulation of the photoactive drug or its metabolites occurs in a smaller percentage of patients after acute

phototoxicity from amiodarone (Ammoury et al. 2008; Kosior 2014), minocycline, imipramine, clozapine, or phenothiazines (Vassileva et al. 1998; Khandpur et al. 2017). Some patients with lower phototypes also develop a golden-brown, slate gray, or bluish color on sun-exposed areas, which persists much longer than residual melanocytic hyperpigmentation (Ammoury et al. 2008; Khandpur et al. 2017).

4.2.4 Other Clinical Patterns

Telangiectasia as a manifestation of photosensitivity has been reported with calcium channel blockers, like nifedipine and amlodipine (Glatz and Hofbauer 2012), and the telangiectatic pattern of photoaging with lesions mainly in the lateral folds of the neck, sparing the shaded rhomboid area under the chin, is frequently observed in patients chronically exposed to the sun and/or photoactive drugs. Petechial purpura with sharp limits on the transition to the shaded areas was described with ciprofloxacin (Urbina et al. 2006).

Pellagra is associated with the prolonged use of isoniazid that consumes niacin for its metabolism, and pellagra-like reactions were reported with the anticancer and immunosuppressive drugs, like 6-mercaptopurine and 5-fluorouracil and azathioprine (Oliveira et al. 2011; Khandpur et al. 2017).

4.3 Delayed and Late Effects of Phototoxicity

Patients that are chronically exposed to photoactive drugs may develop other patterns of skin lesions, like chronic actinic dermatitis and lupus erythematosus where autoimmune reactions are predominantly involved, or accelerated photoaging and skin cancers, which can be explained by the photogenotoxic effect of some phototoxic molecules.

There is a consensual agreement on the increased risk of nonmelanoma skin cancers after long-term therapeutic exposure to PUVA therapy (Stern 2012; Archier et al. 2012) but, apart from psoralens, naproxen, chlorpromazine, and the fluorquinolones, particularly lomefloxacin, also augment in vitro UV-induced DNA aggression and increase epidermal neoplasia in animals (Klecak et al. 1997). Recent reports and epidemiological data also correlate chronic human exposure to photoactive drugs with an increased risk of developing actinic keratoses, nonmelanoma skin cancer, and even, malignant melanoma. In 1999, the group of Przybilla showed an association between actinic keratosis and the use of potentially photosensitizing chemicals (Placzek et al. 1999). More recent studies tend to confirm an increased risk for skin cancer in patients chronically exposed to psoralens, fluoroquinolones, NSAIDs, and diuretics (Jensen et al. 2008) and voriconazole (McCarthy et al. 2007; Epaulard et al. 2013; Goyal 2015). Also, patients with severe chronic photosensitivity develop skin cancers in photoexposed areas, like squamous cell carcinoma with ciprofloxacin (personal experience) and both squamous cell carcinoma and melanoma with voriconazole (Cowen et al. 2010; Miller et al. 2010).

Photoaging, with solar lentigines and actinic keratosis, may also be enhanced by the exposure to topical or systemic photosensitizers.

5 Main Sources of UV Exposure

Recreational and/or occupational sun exposure is the main source of UV radiation for phototoxicity. Farmers, gardeners, construction workers, fishermen, sailors, policemen, ski instructors, oil-field workers, and road workers are occupations where sun exposure can be heavy and prolonged and begin at an early age.

Artificial UV light sources are present in some occupational settings (electric arc welding, solarium and phototherapy units, plants for UV curing of printing inks, lacquers, dental or nail acrylates) and artificial illumination with UVA light-emitting bulbs with no plastic/glass cover may be an additional UVA source.

6 Main Causes of Topical and Systemic Phototoxicity

Plants and drugs are the main causes of phototoxic reactions, but there is a large and increasing list of photoactive molecules, particularly drugs, reported to cause photosensitivity (Table 3).

Table 3 Main agents causing exogenous phototoxicity

Plants	**Umbelliferae**
	Ammi majus
	Apium graveolens (celery)
	Pastinaca sativa (parsnip)
	Petroselinum crispum (parsley)
	Heracleum mantegazzianum (giant hogweed)
	Rutacea
	Citrus spp.
	Citrus aurantica v. bergamia (bergamot)
	Citrus aurantifolia (lime)
	Citrus limon (lemon)
	Ruta graveolans (common rue)
	Dictamus albus (burning bush)
	Moracea
	Ficus carica (fig)
	Hypericaceae
	Hypericum perforatum *(Saint John's wort)*
Drugs	**Antimicrobials**
	Tetracyclines (demeclocycline, doxycycline, minocycline)
	Sulphonamides (sulfametoxazole)
	Fluorquinolones (lomefloxacin[a, b], ciprofloxacin[a, b])
	Voriconazole[b], griseofulvin, efavirenz
	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Arylpropionic acids[a, b]: Ketoprofen, tiaprofenic acid, suprofen, naproxen, ibuprofen, ibuproxam, carprofen
	Benzydamine[a], etofenamate[a]
	Azapropazone, diclofenac, fenilbutazone, indometacine, celecoxib
	Phenotiazines
	Chlorpromazine[a], thioridazine
	Promethazine[a], Chorproethazine[a]
	Antidepressants
	Clomipramine, imipramine, sertraline
	Cardiovascular drugs
	Amiodarone, quinidine, nifedipine, amlodipine, diltiazem
	Furosemide, indapamide and thiazide diuretics[b]
	Anticancer agents
	Paclitaxel, 5-fluoruracil, Dacarbazine, methotrexate, azathioprine, vemurafenib[b]
	Miscellaneous
	Flutamide, sulfonylureas, fenofibrate, simvastatin, pirfenidone, vandetanib

[a]Also reported to cause frequent photoallergic reactions
[b]Associated with enhanced photocarcinogenesis

UV filters, particularly the benzophenones, butylmethoxydibenzoylmethane, octocrylene, and cinnamates, represent the main topical photosensitizers diagnosed by photopatch testing (Darvay et al. 2001; Sheuer and Warshaw 2006; Cardoso et al. 2009; EMCPPTS Taskforce et al. 2012), but they represent almost exclusively contact allergic, photoallergic, or photoaggravated reactions; therefore, they will not be further referred.

In recent decades, premarketing assessment of the phototoxic potential of cosmetics, consumer products, and drugs has been reinforced, and many photosensitizers have been removed or highly reduced in our ambience. Some are now considered "historical" photosensitizers: musk ambrette and natural bergamot oil removed from perfumes; the sunscreens isopropyl–dibenzoylmethane, withdrawn in 1994, and PABA (para-aminobenzoic acid) which sensitized about 4% of the American population in the 1950s (Lowe 2006), are no longer used; olaquindox, an antibiotic added to swine feed, was banned in 1998 by the European Commission (Emmert et al. 2007); the halogenated salicylanilides were removed from disinfectants and hygiene products in most countries since 1976, and the phototoxic NSAIDs carprofen and benoxaprofen were before 2000. Nevertheless, even though not available in Europe, these chemicals can be "imported" and still induce photosensitivity (Emmert et al. 2007; Waters et al. 2009; Gonçalo et al. 2013).

6.1 Plants Causing Phytophotodermatitis

Photoactive furocoumarins, e.g., bergapten (5-methoxypsoralen), 8-methoxypsoralen, 5,6 dimethoxyisopsoralen, sphondin (6-methoxy-isopsoralen), and isobergapten (5-methoxy-isopsoralen) run in the sap of several plants in amounts that vary, for instance, according to the seasons. They are beneficial for the plant as a protection against fungus and insects.

Since the antiquity, these substances have been used in folk medicine in the treatment of vitiligo

and, more recently, in photochemotherapy (PUVA). Aromatic oils rich in furocoumarins, used in tanning oils, were considerably reduced, as the accelerated tanning they induce is considered more harmful than protective.

The natural bergamot oil, extracted from the rind of *Citrus bergamia*, previously included in oils and perfumes, was responsible for a very particular type of phototoxic dermatitis, "breloque dermatitis," or berlock dermatitis. It presented as erythema followed by hyperpigmentation in the shape of a pendant, simulating a breloque, usually beginning in the face or upper neck and descending down to the collar. It corresponds to the area of application of the perfume drop and the subsequent dependent draining area. The natural oil of bergamot is no more used in perfumes and breloque dermatitis is an image of the past, but phototoxicity from psoralens is still observed with aromatic citrus oils used in sauna and massages (Lovell 2000; Zink and Ring 2014).

At present, phototoxic dermatitis from psoralens occurs mainly from inadvertent contact with plants, either during recreation or in occupational settings. Main occupational exposures occur in rural workers or gardeners who harvest fruits or vegetables (parsnip, figs) or cut bushes and weeds like common rue (*Ruta graveolens)*, burning bush (*Dictamnus albus*), fig trees (*Ficus carica*) (Gonçalo et al. 1989; Lovell 2000) or giant hogweed (*Heracleum mantegazzianum*), which has become widespread in Poland causing severe occupational cases of phototoxicity (Klimaszyk et al. 2014). Barmen who squeeze and peal the lime (*Citrus aurantifolia*) and other citrus fruits to prepare cocktails in the sunny weather can also develop contact phototoxic dermatitis, usually with less severe lesions (Wagner et al. 2002; Gonçalo 2004) (Fig. 4).

In 1934 Oppenheim described the most typical pattern of phytophotodermatitis – *dermatosis bullosa striata pratensis* – with prickling linear erythematous skin lesions that correspond to the contact with the damaged leaves of the plant. They develop within 12–48 h after the contact with the plant and sun exposure, may be followed by painful vesicles and bullae (Figs. 5 and 6) and gradually turn into long-lasting brown linear hyperpigmentation, allowing a retrospective diagnosis (Gonçalo 2004).

Other patterns of phytophotodermatitis are the "strimmer dermatitis," a more diffuse involvement as the sap of the plant is sprayed all over the body by the string trimmer, leg dermatitis in walkers who develop lesions only above the socks, and blisters around their mouth in children who make trumpets or pea shooters from the hollow stems of the giant hogweed (*Heracleum mantegazzianum*) (Lovell 2000).

Plants used in "folk medicine" can cause systemic or contact phototoxicity, namely, the ingestion of celery, parsnip, infusions of St. John's wort (*Hypericum perforatum L.*) for depression (Lovell 2000; Schempp et al. 2002; Elkeeb et al. 2012), or the application of infusions of *Ruta graveolens* to relieve pain in fibromyalgia (Arias-Santiago et al. 2009).

Plants causing phytophotodermatitis occur all over the globe and belong mainly to the families of Umbelliferae, Rutacea, and Moracea (Table 3).

6.2 Photosensitive Drugs

Drugs used systemically or applied topically are the main cause of exogenous photosensitivity, particularly in Southern European countries (Leonard et al. 2005; La Cuadra-Oyanguren et al. 2007; Cardoso et al. 2009; EMCPPTS Taskforce et al. 2012). Although most relevant data are from positive photopatch test results that evaluate photoallergy, many of these drugs are also phototoxic.

Drugs manipulated in an occupational setting can induce contact photosensitivity: carprofen in workers who manufacture the drug for animals (Walker et al. 2006; Kerr et al. 2008a), chlorpromazine in nurses and family members who smashed the tablets of to give their patients/relatives (Cardoso et al. 2009; Monteagudo-Paz et al. 2011), and olaquindox or cotrimoxazole in farmers who contact pig or rabbit feed (Emmert et al. 2007; Watanabe et al. 2009).

Systemic drugs that more frequently cause phototoxicity include antimicrobials, antifungals, NSAIDs, phenothiazines, cardiovascular and

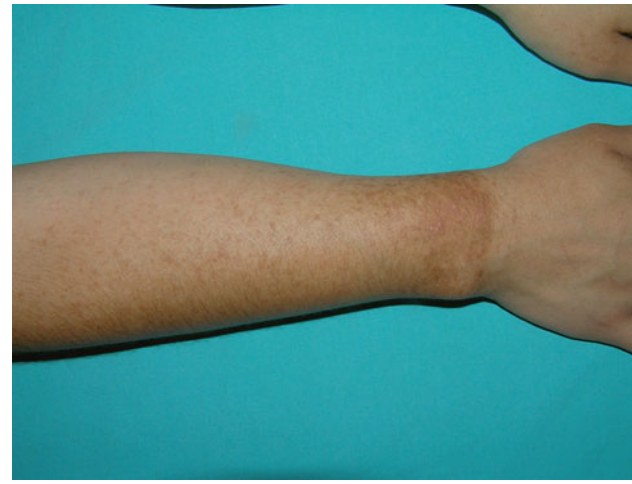

Fig. 4 Residual pigmentation in the forearms in a barman who squeezed limes and lemons for cocktails, during an outdoor summer festival (note limit due to glove protection)

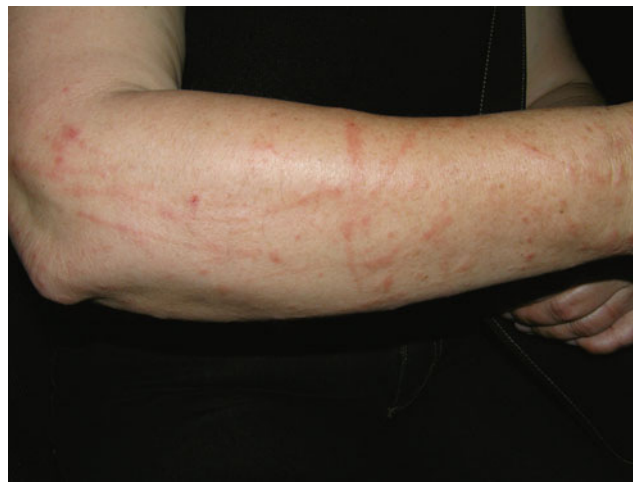

Fig. 5 Phytophotodermatitis with linear streaks of erythema and hyperpigmentation in a patient who contacted Ruta graveolens from her garden

anticancer drugs, and a miscellaneous group (Glatz and Hofbauer 2012; Dawe and Ibbotson 2014; Monteiro et al. 2016). After topical application, NSAIDs are by far the most frequent cause of photosensitivity, mostly photoallergy (Leonard et al. 2005; La Cuadra-Oyanguren et al. 2007; Cardoso et al. 2009; EMCPPTS Taskforce et al. 2012).

6.2.1 Antimicrobials

Systemic tetracyclines, doxycycline, and particularly demeclocycline, are highly phototoxic and induce exaggerated sunburn, photoonycholysis, and pseudoporphyria (Vassileva et al. 1998; Kuznetsov et al. 2011). Minocycline, though less phototoxic, can also induce a bluish persistent pigmentation and has caused photoonycholysis, like lymecycline (Wlodek and Narayan 2014; Monteiro et al. 2016).

The fluorquinolones with an halogen at C-8 (fleroxacin, lomefloxacin, sparfloxacin, pefloxacin) frequently induce phototoxic reactions (4–15% of treated patients), which are less frequent with ciprofloxacin, norfloxacin, ofloxacin, and enoxacin (Monteiro et al. 2016). Like the first quinolone, nalidixic acid, ciprofloxacin has caused

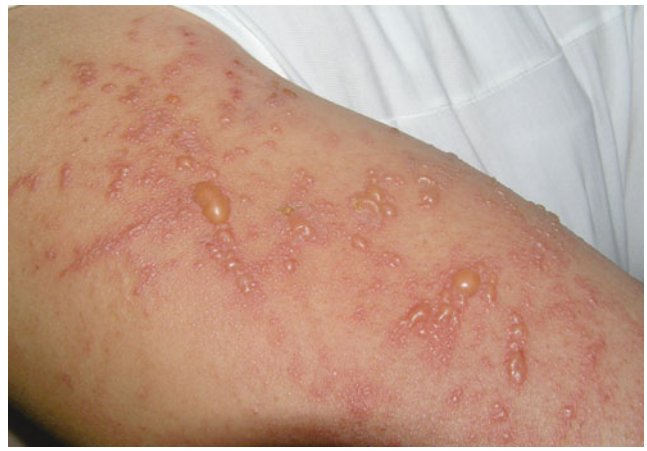

Fig. 6 Phytophotodermatitis with linear bullous lesions in the arms, after cutting a fig tree during a sunny day

pseudoporphyria (Vassileva et al. 1998; Schmutz et al. 2008) and also purpura on photoexposed areas (Urbina et al. 2006) and photo-induced Stevens-Johnson syndrome (Moghaddam and Connolly 2014).Although in vitro and in vivo tests prove the high phototoxic potential of fluorquinolones, photoallergy has also been reported with lomefloxacin (Oliveira et al. 1996; Kurumajin and Shono 1992) and enoxacin (Vassileva et al. 1998), sometimes with cross-reaction to other fluorquinolones (ciprofloxacin and flerofloxacin) (Kimura and Kawada 1998; Correia et al. 1994).

Moreover, the fluorquinolones also photosensitize DNA and may be photomutagenic and photocarcinogenic in vitro and in animal experiences (Klecak et al. 1997). In our experience a patient on long-term ciprofloxacin therapy for multiresistant tuberculosis developed photosensitivity and a highly aggressive squamous cell carcinoma of the face (personal experience).

Sulfonamides, sulfa-drug analogs (thiazide diuretics, hypoglycemic sulfonylureas, and celecoxib), and dapsone (diaminodiphenylsulfone) have been reported to cause photosensitivity within the spectrum both of UVB and UVA, but this side effect is not so frequent with cotrimoxazole (Vassileva et al. 1998; Yazici et al. 2004).

Grisefulvin is a known phototoxic drug that can aggravate lupus erythematosus, and terbinafine induced Rowell syndrome with photo-distribution of skin lesions and subacute lupus erythematosus in patients with anti-Ro antibodies (Farhi et al. 2006; Murad et al. 2015).

Voriconazole is the only triazole antifungal consistently associated with severe phototoxicity that can affect more than 40% of patients, particularly children treated longer than 4–6 months (Goyal 2015; Sheu et al. 2015). Voriconazole phototoxicity presents initially as exaggerated sunburn, cheilitis, pseudoporphyria (Tolland et al. 2007; Frick et al. 2010) and within 1 or 2 years as accelerated photoaging with solar lentigines, actinic keratosis, and enhanced photocarcinogenesis, with the occurrence of multiple and aggressive nonmelanoma skin cancers and also malignant melanoma (Auffret et al. 2006; McCarthy et al. 2007; Cowen et al. 2010; Miller et al. 2010; Goyal 2015; Epaulard et al. 2013). A metabolite of voriconazole – N-oxide-voriconazole – formed in the liver but possibly also in skin cytochromes, and other photoproducts of voriconazole under UVA exposure have been shown to be responsible for phototoxicity and photocarcinogenesis (Haylett et al. 2013; Goyal 2015). The immunosuppressed background of most patients that need long-term voriconzaole treatment may also enhance cutaneous carcinogenesis, but the type and aggressive behavior of the skin cancers related to voriconazole are distinct from those described in organ-transplanted or other immunosuppressed patients, therefore

reinforcing the effect of the drug (Epaulard et al. 2013).

6.2.2 Nonsteroidal Anti-inflammatory Drugs

Benoxaprofen marketed between 1980 and 1982 called the attention to photosensitivity from this class of drugs. Thereafter, photosensitivity was reported with all the other arylpropionic derivatives (carprofen, naproxen, suprofen, tiaprofenic acid, ketoprofen, and ibuprofen), particularly for tiaprofenic acid, which induced typical toxic reactions in more than half of the patients photopatch tested with tiaprofenic acid (5% pet) and 5 J/cm ^{2} of UVA (Gonçalo and Figueiredo 1992; Figueiredo 1994; Neumann et al. 2000). NSAIDs from other groups (azapropazone, diclofenac, piroxicam, fenilbutazone, celecoxib, benzydamine, and etofenamate) have been associated with photosensitivity.

Ketoprofen and piroxicam cause most cases of photosensitivity (EMCPPTS Taskforce et al. 2012; Gonçalo et al. 2013), particularly photoallergy and with a peculiar pattern of cross-reactions with contact allergens or photoallergens (Imai et al. 2005; Béani 2009; Cardoso et al. 2009): cinnamic alcohol, oxybenzone, octocrylene, and fenofibrate for ketoprofene (Pigatto et al. 1996; LeCoz et al. 1998; Devleeschouwer et al. 2008; Foti et al. 2008; Avenel-Audrun et al. 2010), and thimerosal and thiosalicylic acid for piroxicam (Gonçalo et al. 1992; Hariva et al. 1993).

Chronic use of phototoxic NSAIDs has also been associated with enhanced photocarcinogenesis, including malignant melanoma (Siiskonen et al. 2013)

6.2.3 Other Drugs as Photosensitizers

Phenothiazines used systemically (chlorpromazine and thioridazine) can induce photosensitivity, often with a lichenoid pattern and with residual pigmentation (Ferguson 1999). They are typically phototoxic but photoallergy occurs frequently when promethazine is used as topical antipruritic (Cardoso et al. 2009; Katsarou et al. 2008) or chlorproethazine cream is used for muscle pain (Barbaud et al. 2001a; Kerr et al. 2008b).

The antiarrhythmic amiodarone is a well-known photosensitizer. Apart from erythema in sun-exposed areas, it induces a bluish-gray hyperpigmentation in sun-exposed areas due to the accumulation of drug metabolites in the dermis (Ammoury et al. 2008; Kosior 2014). Other cardiovascular drugs have been associated with photo-induced reactions, like amlodipine and nifedipine (telangiectasia), diltiazem (lichenoid reaction with hyperpigmentation), the thiazide diuretics, and furosemide/torsemide (pseudoporphyria, subacute lupus erythematosus, photoonychoysis).

Some anticancer drugs are also associated with photo-induced lesions, like methotrexate (sunburn recall reaction), 5-fluoruracil, 6-mercaptopurine and azathioprine (pellagra-like reactions), paclitaxel and other taxanes (drug-induced lupus erythematosus) (Lamond et al. 2013), imatinib (pseudoporphyria), vandetanib (Chang et al. 2009; Giacchero et al. 2012), and particularly Vemurafenib used in metastatic melanoma. Photosensitivity occurs in more than 50% of patients under veramufenib therapy and presents as burning and painful sensation with a sharply demarcated erythema and edema that appear still during UV irradiation, resembling solar urticaria, but erythema and edema last longer as in erythropoietic protoporphyria (Dummer et al. 2012; Gelot et al. 2013; Brugière et al. 2014). The mechanism is not yet fully understood, but consistently there is a very low minimal erythema dose (MED) for UVA during therapy that normalizes shortly after its suspension (Dummer et al. 2012; Gelot et al. 2013; Brugière et al. 2014). Studies have shown either normal or elevated erythrocyte porphyrins and reduced PP vitamin (Gelot et al. 2013), whereas others show the capacity of Vemurafenib and its UVA photoproducts to incorporate in cell membranes and generate toxic radicals and singlet oxygen that are lethal to the cells even at very low doses (Teixeira et al. 2016).

Another highly phototoxic drug was approved in 2011 for pulmonary fibrosis – pirfenidone. Photosensitivity can be observed in about 50% of treated patients, but this is a known phototoxic chemical and a warning is included in the bulla (Jiang et al. 2012; Adachi et al. 2015; Gaikwad

and Mukherjee 2016; Papakonstantinou et al. 2016).

There is a never-ending list of drugs that may cause photosensitivity, and new drugs are released, some of them despite a known phototoxic potential. Therefore, whenever a patient has a photosensitive eruption a systematic inquiry for drugs should be carefully conducted.

7 Diagnostic Procedures and Preventive Measures in Phototoxicity

Phototoxicity can have such typical lesions, as in phytophotodermatitis or in exaggerated sunburn after the use of a systemic phototoxic drug, that no further diagnostic procedures are needed. Photopatch and photoprovocation tests will be positive in the great majority of individuals when tested with phototoxic chemicals; therefore, these tests are of little use for confirming the etiology of a phototoxic reaction. Photopatch tests are mainly indicated for the etiologic diagnosis of photallergic contact dermatitis and systemic drug photoallergy (Gonçalo 1998; Barbaud et al. 2001b) but can disclose a hidden photoallergy in a photosensitive reaction.

Photopatch testing should be performed according to a standardized procedure (Bruynzeel et al. 2004), using the baseline photopatch tests series and additional substances according to patient exposure (Gonçalo et al. 2013). Irradiation of one set of allergens at day 1 or day 2 should be performed with 5 J/cm^2 of UVA. Readings should be done immediately after irradiation and also 48 and/or 72 h thereafter (Johansen et al. 2015).

Photopatch test results have to be carefully interpreted. A reaction only in the irradiated side mainly with erythema and edema, without pruritus, exclusively limited to the test chamber area, with very sharp limits that begins shortly after irradiation, has its highest intensity by 24 h and regresses by 48/72 h (decrescendo reaction) with hyperpigmentation, suggesting a phototoxic reaction. A similar reaction may be observed in many individuals tested in the same conditions and, if histology is performed, there are many sunburn cells in the epidermis. On the other hand, a pruritic erythema with vesicles, diffuse limits extending beyond the chamber limit, which increase in intensity until 48–72 h after UV irradiation (crescendo reaction), suggests photoallergy (Neumann et al. 1994). But sometimes the clinical pattern of a positive photopatch test reaction is difficult to interpret, in agreement with the difficulties in the interpretation of clinical cases.

Photoprovocation tests calculating MED by irradiating a 2.5 × 2.5 cm area of the skin with increasing doses of UVA, UVB, or with a selected wavelength using a monochromator can give interesting information, even in systemic phototoxicity. The different MED values when the patient is exposed to the drug and after its suspension confirm that the drug is reducing tolerance to UV and defines the UV spectrum responsible for the reaction and, if irradiation is performed in a skin area pretreated with different sunscreens, the test may evaluate the possible protective effect of a sunscreen and the best UV filter or combination of UV-filters that prevents the phototoxic reaction.

For instance, UV filters that protect against UVA have shown to be effective against vermurafenib phototoxicity (Dummer et al. 2012).

Apart from efficient sunscreens and protective clothing, a reduction of the drug dose or the quantity of UV exposure can prevent some phototoxic reactions. Taking the drug by the end of the day may reduce circulating drug concentrations during midday when UV exposure is more likely, eventually reducing the phototoxic reaction.

8 Conclusions

Phototoxic, photoallergic, and overlapping photosensitive reactions are still a frequent problem. They have a highly polymorphic clinical presentation, with different time courses and variations in the responsible agents, depending on geographic areas and evaluated years. Therefore, the dermatologist must be highly alert to search for a possible involvement of an exogenous chromophore in a photosensitive patient. A correct questionnaire should be conducted (Cazzaniga et al.

2015) and, although not so important in typical phototoxic cases, complementary tests including photopatch and photoprovocation tests may contribute to the final etiologic diagnosis and, consequently, allow an adequate patient advice concerning further eviction of the photosensitizer and related chemicals.

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