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Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences

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Summary

Drug-induced photosensitivity, the development of phototoxic or photoallergic reactions due to pharmaceuticals and subsequent exposure to ultraviolet or visible light, is an adverse effect of growing interest. This is illustrated by the broad spectrum of recent investigations on the topic, ranging from molecular mechanisms and culprit drugs through epidemiological as well as public health related issues to long-term photoaging and potential photocarcinogenic consequences. The present review summarizes the current state of knowledge on the topic while focusing on culprit drugs and long-term effects. In total, 393 different drugs or drug compounds are reported to have a photosensitizing potential, although the level of evidence regarding their ability to induce photosensitive reactions varies markedly among these agents. The pharmaceuticals of interest belong to a wide variety of drug classes. The epidemiological risk associated with the use of photosensitizers is difficult to assess due to under-reporting and geographical differences. However, the widespread use of photosensitizing drugs combined with the potential photocarcinogenic effects reported for several agents has major implications for health and safety and suggests a need for further research on the long-term effects.

Photosensitivity: mechanisms and impact

The complete depiction of a complex matter such as drug-induced photosensitivity in a single publication seems almost impossible, given the numerous reports on this topic. The present review therefore aims to cover two focal points. These are *(1)* the drugs responsible for photosensitive reactions and their consequences, and *(2)* the mechanisms of phototoxicity.

Drug-induced photosensitive skin reactions are adverse drug reactions of significant interest. The first reports mentioning occurrence of dermatitis following contact with angelica or parsnips appeared in 1897 [1]. Photosensitive adverse events are usually categorized as either phototoxic or photoallergic, and additionally as either topical or systemic. While this classification is based on different pathophysiological mechanisms, several features illustrate the contrast between them, including incidence, immunization, onset after exposure and clinical appearance [2]. Photosensitizing agents are exogenous chromophores that absorb photons, commonly from solar radiation, leading to their activation and chemical reactions [3]. Photosensitive reactions are limited to specific parts of the electromagnetic spectrum, and occur mainly in the UVA range (wavelength 315–400 nm), although some drugs produce photosensitivity upon exposure to UVB radiation (280–315 nm) or even visible light (400–740 nm). A combined effect of different wavelengths has also been described [4].

Phototoxic reactions

Phototoxic reactions have a higher incidence than photoallergic reactions and can theoretically occur in any individual exposed to the respective agent and radiation, if the dose of either of the two involved factors exceeds a critical threshold [2, 5, 6]. Phototoxic reactions are a dose-dependent phenomenon with respect to both the drug and light exposure [7, 8]. The skin reactions vary depending on the responsible photosensitizer and its respective intracellular target, with some sensitizers even affecting multiple sites [9]. Erythema is the most common clinical manifestation and can be categorized according to its onset as immediate, delayed (12–24 h) or late-onset erythema (24–120 h). Delayed-onset erythema is often referred to as with "exaggerated sunburn". Immediate reactions include burning or prickling sensations and edema. Hyperpigmentation and telangiectasia are additional long-term features. Pseudoporphyria and photo-onycholysis are rare but severe manifestations [9–11]. Phototoxic tissue damage is characterized histologically by dermal edema, dyskeratosis and necrosis of keratinocytes, in severe cases even pan-epidermal [1, 12]. Especially in the case of pseudoporphyria the agents seem to concentrate at the dermo-epidermal junction [9]. Due to its non-immunological nature, phototoxicity can only occur in skin areas receiving light [13]. Delineation of clothing and its shading capacity is an important clinical feature when making a diagnosis [10].

Mechanisms of phototoxic skin damage

There are several pathways that ultimately lead to the observed phototoxic skin response, but initiation of a phototoxic drug reaction always starts with the absorption of UV radiation or visible light. When this happens, the molecule shifts a valence electron to the first available outer shell, thus abandoning its ground state and transforming to an excited state that is chemically unstable. The two following major photochemical pathways involve either an excited triplet state or free radicals. The excited triplet cascade leads to a transfer of energy, either directly to biomolecules or molecular oxygen, thus creating excited singlet oxygen, which corresponds to reactive oxygen species (ROS) [14, 15]. Oxidation of cellular lipids damages cellular components, which results in the clinically apparent skin reaction. Free radicals act by electron transfer, since they have an unpaired valence electron. This then leads to molecular changes of cellular components, which may result in a cytotoxic cellular burden and induce a macroscopically visible phototoxic skin reaction. Interaction of these free radicals with oxygen can also result in the generation of reactive oxygen species [10]. Formation of stable photoproducts by covalent binding of the photosensitizing agent to critical cell compartments and DNA can also cause tissue damage [16]. Figure 1 illustrates the different pathways of photosensitivity schematically.

Reactive oxygen species are generated intracellularly due to various metabolic processes within the mitochondria. ROS have intracellular as well as extracellular functions, and can cause oxidative damage to the cell if its intrinsic antioxidant capacity is exceeded [4]. Since irradiation with UVA light leads to increased ROS generation, keratinocytes have several endogenous enzymatic and non-enzymatic protective antioxidants [17]. These include catalase, glutathione peroxidase and superoxide dismutase to neutralize ROS; higher levels of these are found in the epidermis than in the dermis [18]. Mechanisms to repair damage to DNA and cell membranes as well as to remove damaged proteins have also been discovered [18–20]. With regular sunburn, keratinocytes are forced to undergo programmed cell death [21]. Sunburn is induced primarily by UVB radiation, which causes more direct DNA damage and is slower to repair than ROS damage. However, the majority of phototoxic reactions result from UVA exposure [7, 20, 22].

In general, phototoxic drugs share common features: they have a low molecular weight (between 200 and 500 Daltons) and planar, tricyclic or polycyclic configurations. Their structure may incorporate heteroatoms, which enables resonance stabilization. However, no element or molecule has an automatic ability to induce phototoxicity, although some structural elements, such as aromatic chlorine substituents, are frequently seen in several photosensitizers [10]. Different drugs have different absorption spectra, and therefore have

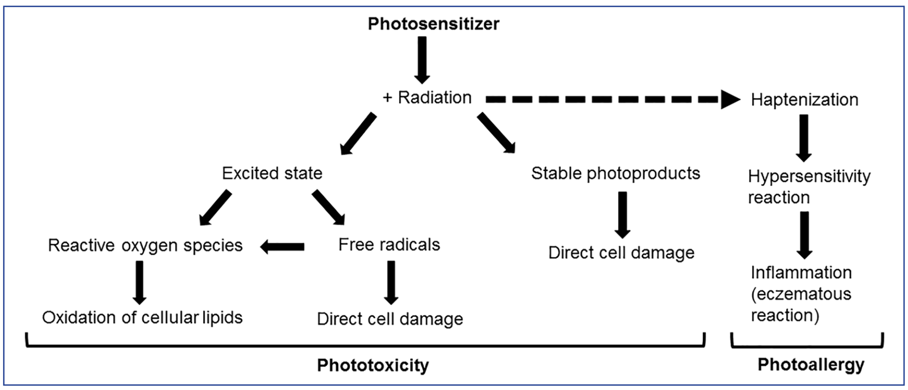

Figure 1 Schematic illustration of the major mechanisms of phototoxic and photoallergic tissue damage.

different action spectra regarding the development of phototoxicity, since the former correspond directly with the latter [2, 23].

Photoallergic Reactions

In photoallergic reactions the photosensitizer absorbs photons, which convert it into a biologically reactive chromophore [24]. This molecule binds to a protein within the dermis or epidermis, forming a complete antigen (haptenization) [25]. Langerhans cells process the antigen and present it *via* MHC II molecules to T cells that reside in lymph nodes. The following response is a homing of activated T lymphocytes into the skin. A photoallergic reaction is therefore a cell-mediated type IV hypersensitivity reaction, and can only occur in previously sensitized patients [25, 26]. Such reactions are rare compared to phototoxic reactions, but have a low threshold dose similar to non-photo-induced cutaneous hypersensitivity reactions [2]. Data regarding the proportion of photoallergic reactions among cases of drug-induced photosensitivity are scarce. However, out of 245 cases of drug-induced photosensitivity diagnosed at the Dundee Photobiology Unit between 1970 and 2000, just a single case (0.04 %) was confirmed as a photo-allergy [9]. Photo-allergies present as eczematous eruptions in areas of skin that are exposed to radiation, but may lack the sharp delineation of phototoxic lesions and do not occur until 24 to 72 hours after exposure [1, 26, 27]. An important feature that distinguishes photoallergic from phototoxic reactions is the typical "crescendo" pattern of the cutaneous manifestations, which is a typical feature of delayed-type hypersensitivity reactions of the skin. This implies that in photoallergic reactions the cutaneous changes increase during the course of the disease, with a peak at about 48–72 hours after the onset of symptoms (crescendo pattern). This is different in phototoxic reactions, where clinical symptoms show a rapid increase to the maximum clinical manifestation after about 24–48 hours of UV exposure, which is followed by a gradual decrease for some days (decrescendo pattern) [1, 28]. The predominant pathogenesis is topically induced photoallergic contact dermatitis, while photo-allergy induced by systemic agents is rather rare [29, 30]. However, a patient sensitized to a topical allergen may develop systemic contact dermatitis following further systemic application of this allergen [31].

Epidemiological burden

It is generally believed that drug-induced photosensitivity is significantly under-reported, due to the difficulty of clinical recognition and the lack of documentation in public databases [4]. The difficulty associated with documentation is increased by the fact that affected patients (and often health professionals) attribute "exaggerated sunburn" to other causes such as excessive sun exposure [32]. The incidence of photosensitive reactions is often reported as up to 8 % of all drug-related cutaneous adverse effects (64 out of 799), based on the retrospective analysis of reports by Selvaag to the Norwegian Adverse Drug Reactions Committee between 1970 and 1994. This amounts to around 0.5 % of all reported side effects [33]. However, these approximations may overestimate the global incidence rates of drug-induced photosensitivity due to two main facts. Firstly, individuals with a fair skin complexion (Caucasian skin type) are more susceptible to phototoxic reactions, while the higher melanin content of darker skins seems to offer some protection [34]. In photoallergic reactions this correlation cannot be observed due to their immunological nature [26]. In a Scandinavian country like Norway, where only 2.4 % of the inhabitants have an African ethnic background associated with a darker skin type [35], this constitutes a significant bias. Secondly, the number also seems to exceed figures reported in other studies. At the Dundee Photobiology Unit, 7 % of all diagnosed photodermatoses from 1970–2000 were classified as drug-induced photosensitivity [9]. Additionally, an analysis of drug-induced photosensitivity using the Japanese Adverse Drug Event Report (JADER) database by Nakao et al. revealed that between 2004 and 2016 only 0.08 % (330 out of 430,587) of all reports concerned photosensitive reactions [36]. When combining these findings, 8 % (and due to under-reporting perhaps more) of all drug-related cutaneous adverse effects appears to be a reasonable upper boundary for drug-induced photosensitivity when focusing on high risk regions. Globally the incidence is likely lower, even in the light of a higher "dark figure". However, these numbers only represent the portion of photosensitive reactions among (clinically apparent) photodermatoses; the incidence of drug-induced photosensitivity itself is not known. In the light of recent reports on the potential carcinogenicity of photosensitive drugs, even subclinical photosensitive reactions may have major health implications when considering chronic drug intake and sun exposure [37]. Therefore, although 7 % of drug-induced photosensitive reactions among all photodermatoses may seem a rather minor health impact, the global impact on health may still be significant. Given the unknown incidence combined with the high dark figure, the following data seem particularly intriguing. A study investigating the number of reimbursed dispensed packages containing potentially photosensitive drugs in Germany and Austria from 2000–2017 based on nation-wide health insurance-based databases revealed that of around 630 million (Germany) and 113 million (Austria) drugs dispensed per year, the mean percentages of photosensitive drugs dispensed were 49.5 % in Germany and 48.2 % in Austria [38]. One might conclude that exposure to potential photosensitizers is substantial, at least in industrialized countries. Given the potential impact of subclinical photosensitivity on carcinogenicity, these numbers raise concern, especially when dealing with increasing rates of chronic drug intake and global sun exposure.

Photosensitizing Drugs

As a result of the growing interest in photosensitive reactions and drugs that induce them, several reviews have been published on drug-induced photosensitivity in the previous twenty years that mention high numbers of relevant drugs and/or drug compounds [3, 9, 10, 26, 39, 40]. The exact number of drugs reported differs substantially between these reviews, but drugs of the following drug classes are present in all published lists of photosensitive drugs: non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobials, antihypertensives and antineoplastic drugs [3, 9, 40]. A study regarding the dispensing rates of photosensitizing drugs in Austria and Germany found a total of 387 different drugs and drug compounds with phototoxic and/or photoallergic reactions [38]. Since this is the largest collection of potential photosensitizers that we are aware of, it served as the basis for development of an updated, even more extensive list summarizing all published photosensitive drugs. Furthermore, a PubMed search using the terms "drug-induced photosensitivity", "drug-induced phototoxicity" and "drug-induced photo-allergy" was conducted to complement the list, resulting in the addition of six drugs in total. Table 1 includes the final list of potential photosensitizing drugs, categorized by drug classes and pharmacological effects. The final compilation consists of 393 different drugs and drug compounds that are potentially photosensitizing, and is therefore the largest of such registers known to the authors to date.

The major limitation of this list is the potential lack of sufficient scientific evidence regarding the photosensitizing potential of several agents. While randomized, double-blind, placebo-controlled trials of possible photosensitizing drugs using standardized photo-testing would be desirable, a recent review by Blakely et al. found that the majority of reports focusing on this issue stem mainly from case reports and case series [40]. Kim et al. concluded in a review that most associations between oral drugs and phototoxicity are not supported by high-quality evidence. Out of 240 eligible studies (with a total of 2,466 subjects), 1,134 cases of suspected phototoxicity were supported by either low or very low-quality evidence, in total 89 % of all studies. Furthermore, they reported that photobiologic evaluation was performed in only 23 % of all studies, and challenge/re-challenge tests were performed in only 10 % of cases [39]. The presented compilation is therefore a list of all potential photosensitizers discussed in the literature, but without a guarantee for completeness.

In addition, a systematic comparative analysis of the photosensitive potential of different photosensitizers would be desirable but is lacking so far. A recent research paper used the number of publications associating an agent with its capability to induce photosensitive cutaneous reactions as an indicator for its photosensitizing potential, which resulted in a "heatmap" of photosensitivity [38]. This indicator is incorporated into Table 1 in order to highlight agents with high numbers ($n \geq 15$) of reports on photosensitivity (shown in bold). Recently discovered photosensitizers (2005 and later) are labeled with an asterisk. Nevertheless, the strongest evidence for the ability to induce phototoxic or photoallergic adverse effects is generally attributed to photo-testing, photopatch testing or re-challenge testing.

Distribution of photosensitizers among drug classes

The 393 agents and compounds that constitute a potential risk of inducing phototoxic or photoallergic reactions (and in some cases both) are summarized in Table 1. The classes that were specified for this review are neither arbitrary nor trivial. The drugs were assigned to a specific class and subclass based on the following principles. Agents were assessed using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Classification established by the WHO Collaborating Centre for Drug Statistics Methodology [41]. There are difficulties associated with ATC codes in that *(1)* some countries establish their own ATC classifications and *(2)* many pharmaceuticals have more than one ATC code attached to them. Nevertheless, the ATC classification used for this review assisted in establishing an initial schematic classification. The drug classes were then merged or newly formed based on their main therapeutic target – to create a final total of seven major drug classes: Cardiovascular, Anti-inflammatory, Antineoplastic, Anti-infectious, Nervous system, Metabolism/Endocrine, and Others (consisting of agents that could not be assigned to any of the above-mentioned groups). The subclasses were then categorized based on their primary indication or molecular target/structure. Again, agents that could not be assigned to any of the subclasses were allocated to their own subclass ("others"). The final classification resembles a clinical approach rather than a pharmacological or chemical classification.

Agents and compounds are not equally distributed among the different drug classes. The largest category is "Nervous system", with 80 drugs, followed by "Anti-infectious" (n = 70) and "Cardiovascular" (n = 60). The group "Anti-inflammatory" contains the lowest number of agents (n = 38). The category "Antineoplastic" is arguably the only drug class where prescription and usage are limited to the

Table 1 A compilation of photosensitizing drugs (total n = 393). Number in brackets indicates the number of agents assigned to the respective drug class/subclass. Agents in bold represent drugs with high evidence of their photosensitizing effects (number of publications n ≥ 15). Asterisks identify agents of which the first report concerning their photosensitizing effects have been published recently (2005 and later).

Cardiovascular (60)			
Diuretics (25)	**Hydrochlorothiazide**	Bendroflumethiazide	Indapamide
	Furosemide	Benzthiazide	Triamterene
	Chlorothiazide	Bumetanide	Chlorothiazide
	Hydroflumethiazide	Butizide	Amiloride
	Methyclothiazide	Cyclothiazide	Torasemide
	Piretanide	Chlorthalidone	Xipamide
	Polythiazide	Metolazone	Ethacrynic acid
	Trichlormethiazide	Quinethazone	Acetazolamide
	Bemetizide		
RAAS effecting (15)	Enalapril	Benazepril	Spironolactone
	Ramipril	Lisinopril	Losartan
	Quinapril	Moexipril	Olmesartan*
	Captopril	Valsartan	Telmisartan*
	Fosinopril	Candesartan*	Irbesartan*
Antiarrhythmics (11)	**Amiodarone**	Diltiazem	Quinidine
	Dronedarone*c	Verapamil	Propranolol
	Disopyramide	Carvedilol	Sotalol
	Procainamide	Tilisolol	
Ca^{2+}-channel antagonists (2)	Amlodipine	Nifedipine	
Antihypertensives (4)	Hydralazine	Diazoxide	Methyldopa
	Rilmenidine	Oxerutins	
Others (3)	Clopidogrel		Triflusal
Anti-inflammatory (38)			
NSAIDs (28)	**Naproxen**	Bexaprofen	Benoxafen
	Ketoprofen	Diflunisal	Indoprofen
	Tiaprofenic acid	Nabumetone	Indomethacin
	Piroxicam	Benzydamine	Fenoprofen
	Carprofen	Flurbiprofen	Sulindac
	Aceclofenac	Ketorolac*	Suprofen
	Diclofenac	Meclofenamate	Ibuprofen
	Mefenaminic acid	Nalidixic Acid	Tolmetin
	Phenylbutazone	Oxaprozin	Mesalazine
	Leflunomide		
COX-2 inhibitors (6)	Celecoxib	Rofecoxib	Nimesulide
	Etodolac	Meloxicam	Valdecoxib
Others (4)	Heroin	Pentosan polysulfate	Achillea millefolium
	Gold		
Antineoplastic (47)			
Alkylating (4)	Hydroxyurea	Dacarbazine	Chlorambucil
	Procarbazine		
Antimetabolite (9)	**Methotrexate**	Pentostatin	Thioguanine
	Mercaptopurine	Tegafur/Uracil	Tegafur/Gimeracil/Oteracil
	Capecitabine	Tegafur	Fluorouracil
Anti-microtubule (3)	Vinblastine	Docetaxel	Paclitaxel
Anthracycline (1)	Epirubicin		

Continued

Table 1 Continued.

Small molecule inhibitors (14)	**Vemurafenib***	Cobimetinib	Regorafenib*
	Vandetanib*	Crizotinib*	Erlotinib*
	Dabrafenib*	Dasatinib*	Imatinib*
	Gefitinib*	Canartinib*	Alectinib
	Lapatinib*	Trametinib*	
Topoisomerase inhibitor (1)	Irinotecan		
Monoclonal antibodies (6)	Nivolumab*	Cetuximab*	Trastuzumab*
	Eculizumab*	Panitumumab*	Mogamulizumab*
Others (9)	Flutamide	Bicalutamide*	Rucaparib
	Midostaurin	Mitomycin	Anagrelide
	PEG Interferon*	Interferon alpha	Arsenic
Anti-infectious (70)			
Fluorquinolones (16)	**Lomefloxacin**	Ulifloxacin	Ofloxacin
	Enoxacin	Grepafloxacin	Trovafloxacin
	Ciprofloxacin	Gemifloxacin	Gatifloxacin
	Clinafloxacin	Levofloxacin	Moxifloxacin
	Sparfloxacin	Fleroxacin	Norfloxacin
	Pefloxacin		
Tetracyclines (7)	**Tetracycline**	Minocycline	Chlortetracycline
	Doxycycline	Oxytetracycline	Lymecycline
	Demeclocycline		
Sulfonamides (5)	Sulfamethoxazole	Sulfadiazine	Sulfasalazine
	Cotrimoxazole	Sulfisoxazole	
Cephalosporins (3)	Cefazolin	Ceftazidime	Cefotaxime
Aminoglycosides (3)	Kanamycin	Streptomycin	Gentamicin
Antimycotics (6)	**Griseofulvin**	Terbinafine	Itraconazole
	Voriconazole	Ketoconazole	Rosemary
Antituberculosis (6)	Isoniazid	Ethionamide	Clofazamine
	Pyrazinamide	Ethambutol	Aminosalicylate
Antiviral (11)	Efavirenz	Daclatasvir*	sodium
	Ritonavir	Amantadine	(Val-)Aciclovir
	Saquinavir	(Val-)Ganciclovir	Simeprevir*
	Zalcitabine	Tenofovir	Ribavirin
Others (13)	**Quinine**	Mefloquine	Dapsone
	Chloroquine	Pyrimethamine	Furazolidone
	Hydroxychloroquine	Quinacrine	Methenamine
	Azithromycin	Sulfadoxine	Flucytosine
	Atoraquone/proguanil		
Nervous system (80)			
Antidepressants (23)	**Hypericum**	Escitalopram	Duloxetine*
	Amitriptyline	Paroxetine	Isocarboxazid
	Imipramine	Protriptyline	Phenelzine
	Clomipramine	Fluvoxamine	Tranylcypromine
	Desipramine	Fluoxetine	Amoxapine
	Trimipramine	Sertraline*	Trazodone
	Nortriptyline	Citalopram	Nefazodone
	Doxepin	Venlafaxine*	
Antipsychotics (34)	**Promethazine**	Olanzapine*	Chlorprothixene
	Thioridazine	Clozapine	Chlorpromazine

Continued

Table 1 Continued.

	Fluphenazine	Haloperidol	Perazine
	Perphenazine	Thioxene	Loxapine
	Flupentixol	Trimeprazine	Mesoridazine
	Molindone	Prochlorperazine	Quetiapine
	Pimozide	Trifluoperazine	Risperidone
	Thiothixene	Alprazolam	Eszopiclone
	Ziprasidone	Chlordiazepoxide	Zaleplon
	Meprobamate	Clorazepate	Maprotiline
	Zolpidem	Triazolam	Carisoprodol
	Aripiprazole		
Anticonvulsants/barbiturates (11)	Carbamazepine	Topiramate	Butabarbital
	Lamotrigine	Valproic Acid	Butalbital
	Phenytoin*	Trimethadione	Pentobarbital
	Felbamate	Phenobarbital	
Triptans (4)	Sumatriptan	Zolmitriptan	Almotriptan
	Naratriptan		
Others (8)	**Cevimeline**	Bupropion	Procyclidine
	Methylphenidate	Danazol	Trihexyphenidyl
	Ropinirole	Acamprosate	
Metabolism/endocrinologic (53)			
Statins (5)	Simvastatin	Pravastati*	Rosuvastatin*
	Atorvastatin*	Pitavastatin*	
Fibrates (3)	**Fenofibrate**	Bezafibrate	Clofibrate
Antidiabetics (12)	Chlorpropamide	Gliquidone	Canagliflozin
	Tolbutamide	Glymidine	Sitagliptin*
	Glyburide	Acetohexamide	Metformin*
	Glipizide	Glimepiride	Tolazamide
Proton-pump inhibitor (3)	Esomeprazole*	Pantoprazole	Rabeprazole
Xanthine-oxidase inhibitor (2)	Allopurinol	Febuxostat	
Hormones (6)	Melatonin	Estrogen	Progesterone
	Hydrocortisone	Epoetin Alpha	Ethinyl estradiol
Antihistamines (19)	Mequitazine	Clemastine	Dimenhydrinate
	Repirinast	Dexchlorpheniramine	Cyproheptadine
	Astemizole	Hydroxyzine	Diphenhydramine
	Azatadine	Meclizine	Loratadine
	Brompheniramine	Tripelennamine	Cetirizine
	Chlorpheniramine	Triprolidine	Terfenadine
	Ranitidine		
Antithyroid (1)	Propylthiouracil		
Others (1)	Bergamot		
Others (45)			
Antiseptic (1)	Thimerosal		
Anticholinergic (6)	Scopolamine	Benzatropine	Atropine sulfate
	Hyoscyamine	Glycopyrrolate	Tiotropium*
Cholinergic (1)	Pilocarpine		
PDE5 inhibitors (2)	Sildenafil	Vardenafil	
Photosensitizers (11)	**Porfimer sodium**	Aminolevulinic acid	Dihematoporphyrin
	8-Methoxypsoralen	Temoporfin	Ether
	5-Methoxypsoralen	Verteporfin	Trioxsalen
	Anthracene	Protoporphyrin	Hematoporphyrin

Continued

Table 1 Continued.

Interleukins (1)	Aldesleukin		
Retinoids (4)	Isotretinoin	Acitretin	Etretinate
	Tretinoin		
Antifibrotic (1)	**Pirfenidone***		
Immunosuppressant (6)	Tacrolimus	Omalizumab*	Tocilizumab
	Azathioprine	Colchicine	*Interferon Beta
Chemotherapy adjuvant (1)	Mesna		
Phytotherapy (4)	Ginseng	Hydrastis canadensis	Angelica sinensis
	Ruta		
Additives (3)	Cyclamate	Tartrazine	Saccharin
Antidote (1)	Tiopronin		
Vitamins (2)	Pyridoxin	Acetylcysteine*	
Vaccines (1)	Smallpox		

respective field. Figure 2 illustrates the relative distribution of the seven drug classes and offers a pharmacological perspective. However, this distribution can be misleading from a clinical point of view. The categories "Nervous system" and "Anti-infectious" both comprise several drugs that have been developed historically but have little or no significance in the clinical daily routine. Cardiovascular, anti-inflammatory and endocrinological photosensitizers are currently highly prescribed medications [38]. Additional information regarding the distribution of agents and subclasses is shown in Supplementary Figure 1. The compilation and classification of photosensitizing drugs is primarily of academic interest since it provides no information on actual usage.

Clinical Consequences

Diagnosis and Management

Patients developing photodistributed erythema (especially after apparently mild exposure to sunlight) should always be regarded as potential cases of photosensitivity. Diagnosis of photosensitive drug eruptions relies on obtaining a detailed medical history, in particular the chronology of medication with respect to the onset of the event [40]. Due to the various presentations of phototoxic and photoallergic reactions, inquiring into potential photosensitizers in the patient's history is mandatory. Furthermore, differential diagnosis between phototoxic and photoallergic reactions is important, since the two reactions require different treatment and different strategies for preventing relapses. The macroscopic presentation of phototoxically damaged skin tends to reveal sharp lines of demarcation of shading clothes, but these lines can be blurred with photo-allergies. Additionally, phototoxic reactions are more common with systemic drugs, while photo-allergies nearly always occur after topical administration. Treatment of photosensitive eruptions should always be initiated by complete avoidance of the causative drug. In cases where the medication is indispensable to the patient, phototoxic effects can be minimized or prevented by dose reduction of either the drug or UV radiation. In photo-allergies this is not feasible due to their immunological nature. Furthermore, photoprotective measures such as sunscreen and UV-blocking clothing are necessary as a supplementary action. Appropriate topical steroids are an option for acute phototoxic cases. Photoallergic reactions may be treated in the same way as allergic contact dermatitis, with topical steroids, antihistamines and NSAIDs as primary treatment options [1, 9, 10]. Appropriate tests for phototoxic reactions are usually reserved for unclear cases, since (at least in theory) all individuals develop them given enough exposure. However, suspected photoallergic dermatitis can be further investigated and confirmed with photopatch testing [11].

Photocarcinogenic Effects of Phototoxic Pharmaceuticals

Drug-induced photocarcinogenesis is a result of taking photosensitizing medication. This is an ongoing problem and the subject of controversial scientific discussions. Even if several specific agents have been associated with photocarcinogenesis, probable mechanisms are still under investigation [32] and subject to debate [38]. The relationship between the use of photosensitive drugs and an increased risk of developing skin cancer is probably multifactorial. Such factors include susceptibility to solar radiation, patient age, cumulative dose and/or duration of treatment as well as other factors as yet unknown [42]. Furthermore,

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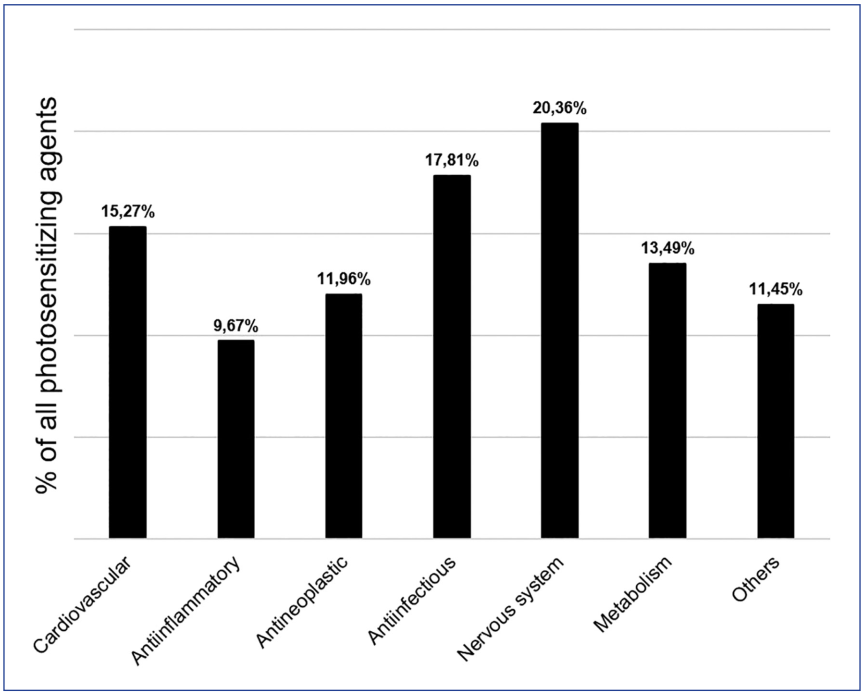

Figure 2 Relative share of potential photosensitizers per major drug class.

the absorption spectrum of the administered drug has been related to the histologic type of skin cancer. For example, amiloride (a diuretic with a maximal absorption in the UVA spectrum) has been associated with a dose-dependent increase in the rate of developing squamous cell carcinomas (SCCs) [43]. However, these investigations mostly represented associative analyses, and proof of a causative role of specific photosensitizing drugs in inducing a specific type of skin cancer due to a specific absorption spectrum has only been shown in sporadic cases. A moderate number of phototoxic drugs has already been associated with photocarcinogenesis in various epidemiological studies and in some cases even involving entire drug classes [43–45]. However, the quality of evidence for single agents is quite diverse. The strongest evidence for photocarcinogenic effects exists for psoralens (furocoumarins), for which the effects have been investigated in animal and human models. This includes studies that demonstrate increased risks of SCC [46], basal cell carcinoma (BCC) [47], and melanoma [48]. Other drugs for which an increased risk of skin cancer has been reported include: NSAIDs and fluoroquinolones [45], thiazide diuretics [43, 44, 49, 50], tetracyclines [44], amiloride [43], amiodarone [51, 52], azathioprine [53, 54], vemurafenib [55, 56] and voriconazole [57, 58]. The increased risk of skin cancer after administration of photosensitizing drugs is likely higher for SCC and melanoma than for developing BCC, although for certain drugs there are studies that suggest an increased risk for BCC as well, such as amiodarone, ciprofloxacin or tetracycline [44, 59]. However, the available data are conflicting in several cases. For example, use of NSAIDs has been associated with a decreased risk of SCC and melanoma, especially with long-term use [60]. To summarize, it can be stated that although there seems to be conflicting epidemiological data on the photocarcinogenic risk of long-term prescription of photosensitizing drugs, an increasing number of studies demonstrate that there is probably a positive correlation between phototoxicity and photocarcinogenesis that requires particular caution with immunocompromised or immunosuppressed patients [4, 32]. Future studies on this question are urgently needed, in particular when considering the potential impact of photosensitizing and/or photocarcinogenic drugs on the health of aging populations with increasing rates of drug prescription.

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