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ORIGINAL ARTICLE

The frequency of photosensitizing drug dispensings in Austria and Germany: a correlation with their photosensitizing potential based on published literature

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Abstract

Background Drug-induced photosensitivity refers to the development of cutaneous adverse events due to interaction between a pharmaceutical compound and sunlight. Although photosensitivity is a very commonly listed side-effect of systemic drugs, reliable data on its actual incidence are lacking so far.

Objectives A possible approach to evaluate the real-life extent of drug-induced photosensitivity would be an analysis of the frequency of exposure to a given photosensitizing drug combined with an indicator of its photosensitizing potential. This could serve as a basis for developing a pharmaceutical 'heatmap' of photosensitivity.

Methods The present study investigated the number of reimbursed dispensed packages of potentially photosensitizing drugs in Germany (DE) and Austria (AT) between 2010 and 2017 based on nationwide health insurance-based databases. In addition, an indicator for the photosensitizing potential was established for each drug based on the number of reports on photosensitivity in the literature.

Results This analysis includes means of 632 826 944 (+/–14 894 918) drug dispensings per year in DE and 113 270 754 (+/–1 964 690) in AT. Out of these, the mean percentage of drugs that enlist photosensitivity as a potential side-effect was 49.5% (± 0.7) in DE and 48.2% (± 1.2) in AT. When plotting the number of reimbursed dispensed packages vs. the number of reports on photosensitivity, two categories of drugs show high numbers for both parameters, that is diuretics and non-steroidal anti-inflammatory drugs (NSAIDs).

Conclusions Diuretics and NSAIDs appear to be responsible for the greatest part of exposure to photosensitizing drugs with potential implication on public health.

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Conflict of interest

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Introduction

Drug-induced photosensitivity refers to the development of cutaneous adverse events due to interaction between a given pharmaceutical compound and sunlight. Photosensitizing drugs act as exogenous chromophores that are transformed by absorption of photons into a photochemically active excited state and subsequently undergo chemical reactions.¹ Manifestations of drug-induced photosensitivity can be subdivided into phototoxic and photoallergic reactions. The action spectrum mostly lies within the UVA range although some drugs are activated by visible light or UVB radiation or a combination of

different wavelengths.² The mechanisms for tissue damage in phototoxicity involve oxidation of cellular lipids, proteins and DNA, often mediated by reactive oxygen species (ROS),^{3,4} or formation of stable photoadducts.⁵ Photoallergy represents a T-cell-mediated delayed-type hypersensitivity reaction that involves covalent binding of a pharmaceutical compound to an endogenous protein in the presence of solar radiation.² The great majority of reactions to systemic drugs are phototoxic in nature, whereas topical agents such as chemical UV filters or non-steroidal antirheumatics are the main causes of photoallergic reactions.^{6,7}

Up to the present, a vast number of drugs have been associated with photosensitivity and the number is increasing every year.⁸ In particular, antimicrobials, non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular agents and psychotropics have been implicated in photosensitive reactions.¹ In general, the elderly population is at higher risk given its greater consumption of different drugs for the treatment of chronic diseases.⁹ Besides acute cutaneous adverse effects, an increasing number of reports also suggest chronic sequelae such as increased photoaging or photocarcinogenesis.^{8,10} However, as yet this is still a matter of controversial scientific discussions.

Although drug-induced photosensitivity is considered to account for up to 8% of reported cutaneous adverse events from drugs,^{1,11} reliable data on its actual incidence are lacking so far. It is generally assumed that drug-induced photosensitivity is heavily underreported owing to a lack of clinical recognition and a lack of reporting to databases.² This most probably results in an appreciable number of underdiagnosed and underreported cases hampering retrospective analyses of the true incidence of drug-induced photosensitivity. A possible approach to evaluate the actual incidence of drug-induced photosensitive reactions would be an analysis of the 'societal exposure' of photosensitizing drugs combined with an indicator of their photosensitizing potential. This could serve as a basis for delineating the photosensitizing potential of currently prescribed systemic drugs.

In the present study, we investigated the number of reimbursed, dispensed packages of photosensitizing drugs in Germany and Austria between 2010 and 2017 based on nationwide health databases on drug dispensings. These data were directly correlated with an indicator of the photosensitizing potential of each drug. With this approach, we aimed at identifying drugs that have both, high dispensing rates and a high photosensitizing potential, and thus the greatest bearing on drug-induced photosensitivity reactions.

Methods

Study design and source of data

The present work was designed as a drug utilization study targeting at the analysis of the dispensings of photosensitizing drugs within defined timely and regional boundaries. The German data set was provided by the *German Institute for Drug Use Evaluation* (DAPI, Berlin, Germany) which collects anonymous claims data of drugs prescribed and subsequently dispensed at community pharmacies at the expense of the Statutory Health Insurance (SHI) Funds.¹² Nearly 87% of Germany's (DE's) population is insured by the SHI system.^{13,14} The DAPI data cover 80% of the community pharmacies in DE and were extrapolated by regional factors to 100% of the SHI insured population. The Austrian data set was provided by *The Main Association of Austrian Social Security Institutions* which serves as the umbrella organization of the statutory health insurances in Austria (AT). About 98% of the Austrian population is covered by the statutory health

insurances. All costs exceeding the copayment are covered by the health insurance.^{15,16} Both data sets contained longitudinal data concerning the overall number of rates of dispensed drugs for single (or combined) agents within a given time frame in the respective country. Both data sets do not include drugs dispensed in hospital (inpatient) settings. For additional information, please refer to the Appendix S1 (Supporting Information).

Compilation of photosensitizing agents

To create a most complete and actual list of photosensitizing drugs, we first referred back to the compilations published in review articles by Moore,⁸ Drucker and Rosen¹⁷ as well as Monteiro *et al.*¹ since they seemed to provide the most complete recent overviews on that subject. In addition, *Litt's Drug Eruption & Reaction Database* was consulted and further drugs (not mentioned in the review articles) were added to the list. Drugs listed in the database under the label 'photosensitivity' were added to the list of photosensitizing drugs. Finally, a MEDLINE search for the terms 'photosensitivity' as well as 'phototoxic'/'photoallergic' was performed in November 2017 in order to complement the initial overview. For additional information, please refer to the Appendix S1 (Supporting Information).

Development of an indicator for photosensitivity

The incidence of photosensitive adverse reactions of a given pharmaceutical compound is the product of its prescription frequency and its photosensitizing potential (though further factors such as the UV spectrum, exposure dose, climate area or season of exposure may also have an influence). With regard to the latter, an indicator for each drugs' photosensitizing potential had to be established. So far no comparative clinical or experimental studies have been performed addressing the difference in the photosensitizing potential across a large series of different pharmaceutical compounds. This may be due to the many factors influencing the clinical manifestation as well as the magnitude of different compounds. Based on the assumption that there is a correlation between the number of reported photosensitive side-effects and the photosensitizing potential of a given drug, we established the number of publications reporting a photosensitive adverse drug reaction as an indicator for the photosensitizing potential of a drug. To this purpose, a MEDLINE search was performed between April 2018 and December 2018 to systematically identify all reports for every drug mentioned in the list above. Importantly, this analysis was only performed for drugs that were actually prescribed in DE and/or AT within the observational period. For this analysis, the search term 'photosensitivity' in addition to each single drug name was used since this would address both, reports on phototoxic and photoallergic side-effects. Inclusion and exclusion criteria were formulated to determine which publications qualified to be included into the analysis. In a second step, *Litt's Drug Eruption & Reaction Database* was again used to complement the findings derived from

the MEDLINE search in order to achieve a maximum number of reports for each compound listed. The according study flow chart is shown in Fig. 1.

Statistical analysis

The numbers of reimbursed dispensed packages were analysed with regard to overall yearly prescriptions to assess general trends. The agents of interest were categorized according to a classification adapted from the *World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification System*.¹⁸ Descriptive analyses for both – drug groups and single agents – were performed concerning reimbursed drug dispensings, potential of photosensitive adverse reactions and the combination of both features using Microsoft Excel (2016, Microsoft Corp., Redmond, WA, USA). For details on the statistical analyses, please also refer to the Appendix S1 (Supporting Information).

Results

Compilation of photosensitizing agents

Based on published literature and an adverse drug reaction database, a compilation of photosensitizing medications has been established (see Table 1 summarizing all drugs). In total, 387 pharmaceutical compounds could be identified that have been

associated with causing photosensitivity either from literature or by the database. The largest group containing the highest number of compounds was the group 'nervous system', while the group 'anti-infectious' showed the second most and the group 'cardio-vascular' the third most compounds. Out of the 387 agents with photosensitizing potential, 291 agents (75.2%) were dispensed and reimbursed in DE and 220 (56.9%) in AT during the study period. These drugs are highlighted in Table 1 with indications of their use in DE (#) and/or AT (+). Therefore, Table 1 provides both information on which drugs are more likely to cause photosensitivity since they have actually been dispensed (written in bold letters in Table 1) and information on other drugs with photosensitizing potential (non-dispensed/reimbursed).

Frequency of photosensitizing drug dispensings

In the period between 2010 and 2017, the mean total number of reimbursed drug packages dispensed in DE was 632.827 mio. [± 14.895 mio.] per year and in AT 113.271 mio. [± 1.965 mio.] per year. In DE, the total number of dispensed drug packages rose from 617.54 mio. in 2010 to a maximum of 655.351 mio. in 2016 and slightly decreased thereafter to 648.093 mio. in 2017 as presented in Fig. 2a. This corresponds to an increase in drug dispensings of + 4.95% during the study period. In AT, the total number of packages of pharmaceuticals reimbursed in

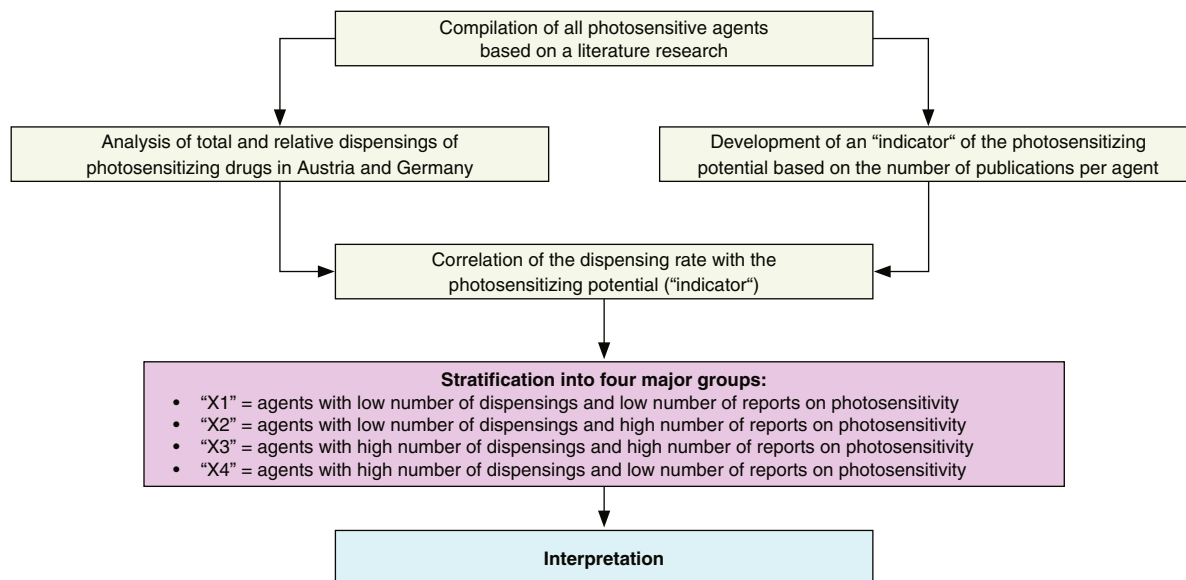


Figure 1 Study flow chart. First, a compilation of all photosensitive pharmaceutical agents was established based on an extensive literature research. In parallel, the total and relative number of reimbursed dispensings of photosensitizing drugs in Austria and Germany was performed. In addition, an 'indicator' of the photosensitizing potential of each drug was determined based on the number of reports on photosensitivity. Finally, the dispensing rate was graphically correlated with the 'indicator' resulting in four different groups of photosensitizing drugs 'X1'–'X4', which served as a basis for the interpretation of the results.

Table 1 Compilation of pharmaceutical compounds with photosensitizing potential

1 Cardiovascular			
Diuretics	Hydrochlorothiazide #+	Bendroflumethiazide #+	Indapamide #+
	Benzylhydrochlorothiazide	Benzthiazide	Triamterene #
	Chlorothiazide	Bumetanide #+	Furosemide #+
	Hydroflumethiazide	Butizide +	Amiloride #
	Methyclothiazide	Cyclothiazide	Torasemide #+
	Piretanide #	Chlorthalidone #+	Xipamide #+
	Polythiazide	Metolazone	Ethacrynic acid
	Trichlormethiazide	Quinethazone	Acetazolamide #+
	Bemetizide #		Spirolacton #+
Agents acting on the renin–angiotensin system	Enalapril #+	Benazepril #	Losartan #+
	Ramipril #+	Lisinopril #+	Omesartan #+
	Quinapril #+	Moexipril #	Telmisartan #+
	Captopril #+	Valsartan #+	Irbesartan #+
	Fosinopril #+	Candesartan #+	
Antiarrhythmics	Amiodarone #+	Disopyramide	
	Dronedarone #+	Procainamide	
Beta blocking agents	Propranolol	Carvedilol #+	
	Sotalol #+	Tilisolol	
Calcium channel blocking agents	Amlodipine #+	Diltiazem #+	
	Nifedipine #+	Verapamil #+	
Other antihypertensives	Hydralazine #	Methyldopa #+	Diazoxide #
	Rilmenidine +		
Antithrombotic agents	Clopidogrel #+		
Others	Oxerutins #	Quinidine #	
2 Anti-inflammatory and antirheumatic products			
Anti-inflammatory and antirheumatic products, non-steroids (excluding Coxibs)	Naproxen #+	Benoxaprofen	Benoxaprofen
	Ketoprofen #+	Diflunisal	Indoprofen
	Tiaprofenic acid #	Nabumetone #	Indomethacin #+
	Piroxicam #+	Benzydamine #+	Fenoprofen
	Carprofen	Flurbiprofen +	Sulindac
	Aceclofenac #	Ketorolac #+	Suprofen
	Diclofenac #+	Meclofenamate	Ibuprofen #+
	Mefenamic acid +	Oxaprozin	Tolmetin
	Phenylbutazone #+	Meloxicam #+	Nimesulide +
	Gold #	Etodolac	
Coxibs	Celecoxib #+	Rofecoxib	Valdecoxib
Others	Heroin	Pentosan polysulphate	Achillea millefolium
	Mesalazine #+	Nalidixic acid	
	Sulphasalazine #+		
3 Antineoplastic and immunomodulating agents			
Alkylating	Dacarbazine #+	Chlorambucil #+	
Antimetabolite	Fluorouracil #+	Pentostatin	Thioguanine #+
	Mercaptopurine #+		
	Capecitabine #+	Tegafur/Uracil #	Tegafur/Gimeracil/
		Tegafur +	Oteracil #
			Methotrexate #+
Plant alkaloids and other natural products	Vinblastine #+	Docetaxel #+	Paclitaxel #+
Anthracyclines and related substances	Epirubicin #+		

Table 1 Continued

3 Antineoplastic and immunomodulating agents			
Protein kinase inhibitors	Vemurafenib #+	Cobimetinib #+	Dabrafenib #+
	Trametinib #+	Crizotinib #+	Erlotinib #+
	Regorafenib #+	Dasatinib #+	Imatinib #+
	Gefitinib #+	Canertinib	Alectinib +
	Lapatinib #+	Vandetanib #+	
Topoisomerase inhibitor	Irinotecan #+		
Monoclonal antibodies	Nivolumab #+	Cetuximab #	Trastuzumab #+
	Eculizumab #+	Panitumumab #+	
Others	Hydroxyurea #	Flutamide #+	Rucaparib
	Procarbazine #	Bicalutamide #+	Anagrelide #
	PEG interferon #+	Midostaurin +	Arsenic #
	Interferon alpha #+		
4 Anti-infectives			
Fluoroquinolones	Lomefloxacin #+	Ulfloxacin +	Ofloxacin #+
	Fleroxacin	Ciprofloxacin #+	Trovafloxacin
	Clinafloxacin	Grepafloxacin	Gatifloxacin
	Sparfloxacin	Gemifloxacin	Moxifloxacin #+
	Enoxacin #	Levofloxacin #+	Norfloxacin #+
	Pefloxacin		
Tetracyclines	Tetracycline #+	Doxycycline #+	Chlortetracycline #
	Oxytetracycline #	Minocycline #+	Lymecycline +
	Demeclocycline #		
Sulfonamides	Sulphamethoxazole	Sulphadiazine #+	
	Cotrimoxazol #+	Sulphisoxazole	
Cephalosporins	Cefazolin #+	Ceftazidime #+	Cefotaxime #+
Aminoglycosides	Kanamycin #	Streptomycin #	Gentamicin #+
Antimycotics	Griseofulvin #	Terbinafine #+	Itraconazole #+
	Voriconazole #+	Ketoconazole #+	Rosemary #
Antimycobacterials	Isoniazid #+	Ethionamide	Clofazimine
	Pyrazinamide #+	Ethambutol #+	Aminosalicylate sodium #+
Antivirals	Efavirenz #+	Daclatasvir #+	Acyclovir / Valaciclovir #+
	Ritonavir #+	Amantadine #+	Simeprevir #+
	Saquinavir #+	Ganciclovir/ Valganciclovir #+	Ribavirin #+
	Zalcitabine		
Others	Quinine #	Mefloquine #+	Dapsone #
	Chloroquine #	Pyrimethamine #	Furazolidone
	Hydroxychloroquine #	Quinacrine	Methenamine #
	Azithromycin #+	Sulphadoxine	Flucytosine #
5 Nervous system			
Antidepressants	Protriptyline	Escitalopram #+	Duloxetine #+
	Amitriptyline #+	Paroxetine #+	Isocarboxazid
	Imipramine #	Hypericum #+	Phenelzine
	Clomipramine #+	Fluvoxamine #+	Tranlycypromine #+
	Desipramine #	Fluoxetine #+	Amoxapine
	Trimipramine #	Sertraline #+	Trazodone #+
	Nortriptyline #	Citalopram #+	Nefazodone
	Doxepin #+	Venlafaxine #+	
		Bupropion #+	

Table 1 Continued

5 Nervous system			
Antipsychotics	Chlorpromazine	Olanzapine #+	Chlorprothixene #+
	Thioridazine #	Clozapine #+	Perazin #
	Fluphenazine #	Haloperidol #+	Loxapine #
	Perphenazine #+		Mesoridazine
	Flupentixol #+	Trimeprazine	Quetiapine #+
	Molindone	Prochlorperazine	Risperidone #+
	Pimozide #+	Trifluoperazine	Maprotiline #+
	Thiothixene	Ziprasidone #+	
	Meprobamate +	Alprazolam #+	
	Clorazepate #	Chlordiazepoxide #	
Hypnotics and sedatives	Zolpidem #+	Triazolam #+	Promethazine #
	Eszopiclone	Butobarbital	Pentobarbital
	Zaleplon #		
Anticonvulsants/Barbiturates	Carbamazepine #+	Topiramate #+	Butobarbital
	Lamotrigine #+	Valproic acid #+	Butalbital
	Phenytoin #+	Trimethadione	Pentobarbital
	Felbamate #+	Phenobarbital #	
Selective serotonin (5HT1) agonists	Sumatriptan #+	Zolmitriptan #+	Almotriptan #
	Naratriptan #+		
Others	Acamprosate #+	Carisoprodol	Procyclidine #+
	Methylphenidate #+	Cevimeline #	Trihexyphenidyl #
	Ropinirole #+		
6 Metabolism/endocrine therapy			
HMG-CoA reductase inhibitors	Simvastatin #+	Pravastatin #+	Rosuvastatin #+
	Atorvastatin #+	Pitavastatin #	
Fibrates	Clofibrate	Bezafibrate #+	Fenofibrate #+
Drugs used in diabetes	Chlorpropamide	Gliquidone #+	Canagliflozin #+
	Glyburide (Glibenclamide) #+	Glymidine	Sitagliptin #+
	Glipizide +	Acetohexamide	Metformin #+
	Tolbutamide	Glimepiride #+	Tolazamide
Proton-pump inhibitors	Esomeprazole #+	Pantoprazole #+	Rabeprazole #+
Antigout preparations	Allopurinol #+	Febuxostat #+	Colchicine #+
Hormones	Melatonin #+	Oestrogen #+	Progesterone #+
	Hydrocortisone #+	Epoetin alpha #	Ethinyl estradiol #+
Antihistamines	Mequitazine #	Clemastine #	Dimenhydrinate #
	Repirinast	Dexchlorpheniramine #	Cyproheptadine #+
	Astemizole	Hydroxyzine #+	Diphenhydramine #+
	Azatadine	Meclizine	Loratadine #+
	Brompheniramine	Tripeleonnamine #	Cetirizine #+
	Chlorpheniramine #	Triprolidine	
	Ranitidine #+	Terfenadine #	
Thyroid therapy	Propylthiouracil #+		
Others	Bergamot #		
7 Others			
Antiseptic	Thimerosal #		
Anticholinergic	Scopolamine #	Benzatropine	Atropin sulphate #
	Hyoscyamine #	Glycopyrrolate #+	Tiotropium #+
Cholinergic	Pilocarpine #+		
PDE ₅ inhibitors	Sildenafil #+	Vardenafil #+	

Table 1 Continued

7 Others			
Photosensitizers	Verteporfin #+	Aminolevulinic acid #+	Dihaematoporphyrin ether
	Protoporphyrin	Porfimer sodium #	Trioxsalen
	5-Methoxypsoralen +	8-Methoxypsoralen #+	Haematophyrin
	Anthracene		
Retinoids	Isotretinoin #+	Acitretin #+	Etretinate
	Tretinoin #+		
Immunostimulants	Aldesleukin #+		
Immunosuppressants	Tacrolimus #+	Omalizumab #+	Interferon beta #+
	Azathioprine #+	Tocilizumab #+	Pirfenidone #+
	Leflunomide #+		
Phytotherapeutics	Ginseng #	Hydrastis canadensis #	Angelica sinensis
	Ruta #		
Additives	Cyclamate #	Saccharin #	Tartrazine #
Antidot	Tiopronin #	Acetylcysteine #+	
Vitamins	Pyridoxine #+		
Vaccines	Smallpox #		

indicates that the compound was dispensed and reimbursed in DE between 2010 and 2017; + indicates that the compound was reimbursed in Austria between 2010 and 2017; and compounds printed in bold were reimbursed in both countries between 2010 and 2017.

the outpatient sector remained relatively stable over the years [increasing from 112.931 mio. in 2010 to a maximum of 115.761 mio. in 2014 and decreasing to 109.073 mio. in 2017 (see Fig. 2b)]. When relating these numbers to the amount of the total number of insured persons per year, a similar picture evolves (Fig. 3c,d).

Out of these total drug dispensings, the mean percentage of photosensitizing agents was 49.5% (± 0.7) in DE and 48.2% (± 1.2) in AT over the entire study period. The overall use of photosensitizing drugs rose from 309.416 mio. in 2010 to 313.161 mio. in 2017 in DE, representing an increase of 3.745 mio, including a peak of 320.021 mio. in 2016 (see Fig. 2e,g,i). In AT, the overall number of photosensitizing drug dispensings was 51 600 780 in 2010 that rose to 57 426 060 in 2014 and decreased to 52 176 413 in 2017 (see Fig. 2f,h,j). These findings reveal that the absolute dispensing rates of photosensitizing drugs were increasing during the initial phase of the observational period in both countries. However, in both countries a decrease in total photosensitizing drug dispensings was observed over the last years (which was much more profound in AT). Interestingly, the relative amount of photosensitizing drug prescriptions (in %) showed a continuous decrease in DE over years, while the number in AT only decreased during the last 3 years (Fig. 3g,h).

Distribution of photosensitizing agents and number of dispensings across drug classes

Photosensitizing drugs differ across drug classes both with respect to the total number of photosensitizing agents per drug class and the frequency of prescriptions per year. The category 'nervous system' contains the highest number of photosensitizing drugs within a category (20.7%), followed by the

categories 'anti-infectious' and 'cardiovascular' drugs (Fig. S1a, Supporting Information). However, when looking at the mean number of photosensitizing drug prescriptions per year in DE, the highest dispensing numbers are found in the category 'cardiovascular' (117.1 mio. dispensings, 33.0% of all dispensings) followed by the category 'metabolism' (85.5 mio. dispensings, 24.1% of all dispensings; see Fig. S1b,c (Supporting Information), number per 1000 insured persons – Fig. 1d). The respective absolute and relative numbers in the AT population are shown in Fig. S1e–g (Supporting Information). Interestingly, the relative distribution in AT is almost identical to the German population (also showing the highest number of dispensings in the category 'cardiovascular', see Fig. S1g, Supporting Information).

The example of the drug class 'cardiovascular' demonstrates that there is often a discrepancy between the number of photosensitive agents and their effective rate of dispensings. While the drug class 'cardiovascular' accounts for 15.2% of all photosensitive drugs, their mean share of all dispensings per year in DE was found to be 33.0%. A similar trend was evident for the drug class 'metabolism' as well as the class 'anti-inflammatory', while other classes showed an inverse trend with a higher share among photosensitive drugs vs. a lower dispensing rate (see Fig. S1a–g, Supporting Information).

Development of an indicator for the photosensitizing potential

A systematic MEDLINE search identified 1697 reports on photosensitivity linked to the 291 agents prescribed in DE and the 220 agents prescribed in AT, respectively, during the observational period. In the Table S1 (Supporting Information), all

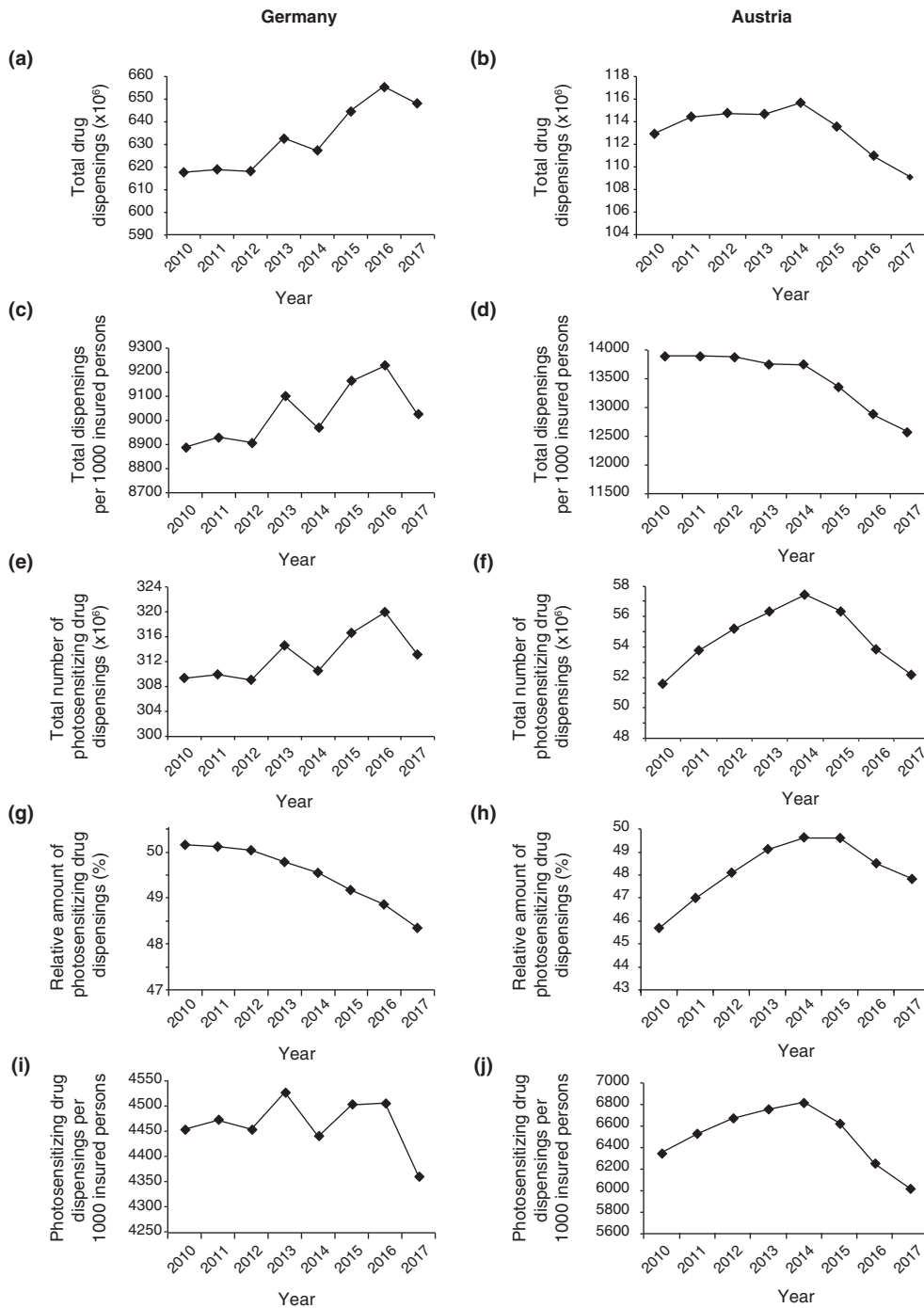


Figure 2 Total and relative number of drug dispensings in Germany (DE) and Austria (AT) between 2010 and 2017. Total amount of all (a–d) and photosensitizing (e–f) drug dispensings. Relative amount of photosensitizing drug dispensings out of all dispensings (in %, g, h) in DE and AT. Total amount of photosensitizing drug dispensings per 1000 insured persons in DE and AT (i, j).

references are summarized and linked to the specific pharmaceutical agent. The highest number of drug-induced photosensitivity reactions was reported for ‘anti-infectious’ drugs

(Fig. S2a, Supporting Information). In Fig. S2b (Supporting Information), the timely evolution of the reports on photosensitivity is summarized.

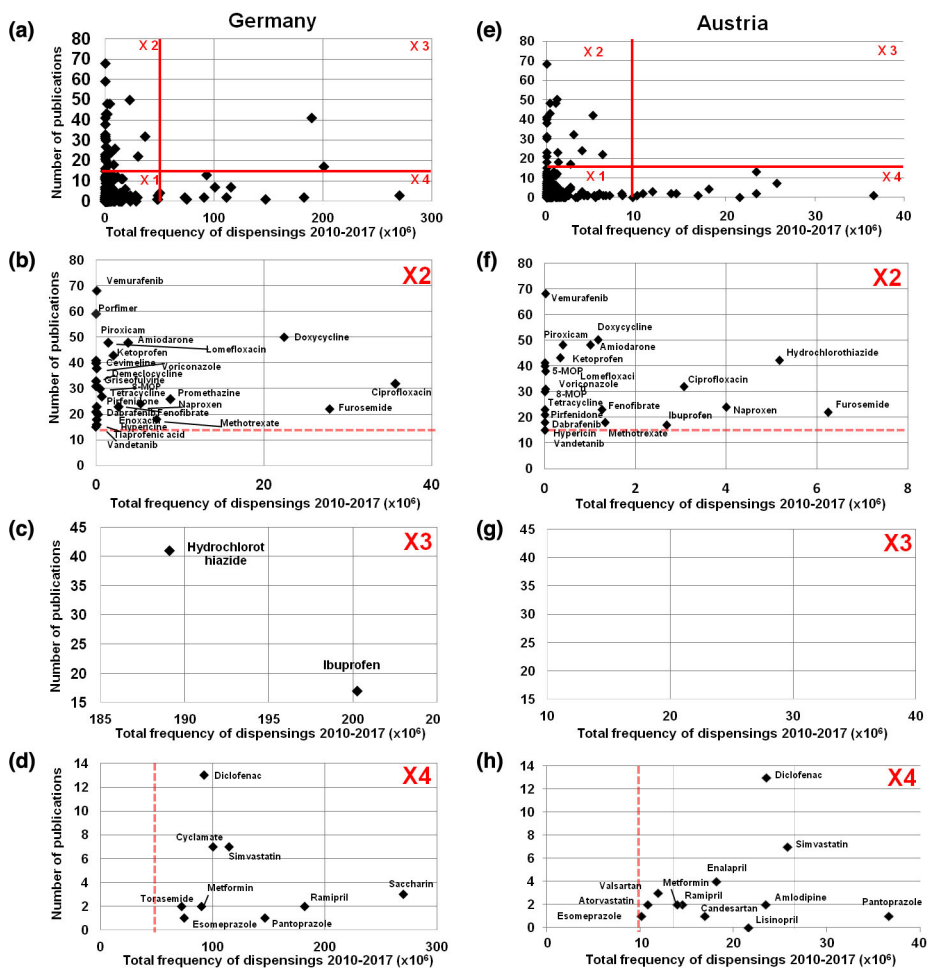


Figure 3 Combined analysis of drug dispensings and reference score. Scatterplot of the total number of dispensings of each single agent plotted against the number of publications (‘reference score’) in Germany (DE) (a–d) and Austria (AT) (e–h). The resulting diagram in (a) and (e) is subdivided into four segments each (‘X1’–‘X4’). In the subfigures b–d and f–h, a detailed analysis of ‘X2’–‘X4’ is shown.

Correlation analysis of the dispensing rate with the publication number

In order to determine the relevance of the absolute prescription number, a correlation analysis with the aforementioned indicator, the number of publications per drug according to the systematic literature search, was performed. Plotting the number of prescriptions vs. the number of reports on cutaneous photosensitivity reactions per agent identifies a small number of drugs with the highest potential for causing photosensitivity in the real-life setting. For a further in-depth analysis, these scatter plots were subdivided into four segments ‘X1’–‘X4’ (see Fig. 3a–h) as described in the Methods. ‘X1’ represents those drugs with the lowest number of dispensings (<50 000 000 over the study period) and the lowest number of reports on photosensitivity (<15 in DE and AT),

thus the group with the lowest significance for photosensitive adverse events (Fig. 3a).

The segment ‘X2’ (Fig. 3b) comprises agents with a well-documented photosensitizing potential (≥15 publications) but a limited dispensing rate (<50 000 000 over the study period). This category represents the prototypical drugs of well-known photosensitizing potential such as vemurafenib, doxycycline or amiodarone. The extracted segment ‘X2’ labelled with the respective drug names is shown in Fig. 3b, and all agents are summarized in Table 2.

Segment ‘X3’ (Fig. 3c) contains drugs with a well-documented photosensitizing potential (≥15 publications) and high dispensing rates (≥50 000 000 over the study period). In DE, only two agents fall into this category, hydrochlorothiazide and ibuprofen. In AT, none of the drugs falls into this segment; however, several

Table 2 All photosensitizing agents ($n = 26$) in segment 'X2' of Fig. 3 with the number of reports on photosensitivity in brackets, used as indicator of the photosensitizing potential

Furosemide (22)	Amiodarone (48)
Naproxen (24)	Vandetanib (15)
Ketoprofen (43)	Lomefloxacin (41)
Tiaprofenic acid (16)	Enoxacin (20)
Piroxicam (48)	Ciprofloxacin (32)
Methotrexate (18)	Tetracycline (30)
Vemurafenib (68)	Demeclocycline (33)
Dabrafenib (21)	Doxycycline (50)
Griseofulvin (32)	Quinine (27)
Voriconazole (38)	Hypericin (18)
Promethazine (26)	Cevimeline (40)
Fenofibrate (23)	8-Methoxypsoralen (31)
Porfimer (59)	Pirfenidone (23)

drugs are close to fit into this segment such as hydrochlorothiazide, furosemide, ciprofloxacin, naproxen and ibuprofen. These two categories of drugs, namely diuretics and NSAIDs, are most likely to cause photosensitivity reactions and are therefore most important from a public health perspective (see Fig. 3c). In addition, prescription of several agents out of these drug groups is increasing between 2010 and 2017 (data not shown).

The segment 'X4' (Fig. 3d) corresponds to drugs with a low number of publications (<15) but a large number of annual dispensings ($\geq 50\,000\,000$ over the study period). Given the limited published evidence for causing photosensitivity, their role as potential photosensitizers seems rather low. The data for the AT study population are shown in Fig. 3e–h.

Discussion

Drug-induced photosensitivity reactions are rarely documented in the published literature. This is partly due to underreporting of affected subjects who might simply stop taking the causative drug or attributing the 'exaggerated sunburn' to other causes, such as excessive sun exposure. In addition, the lack of adequate pharmacovigilance and a publication bias towards publishing only extravagant cases may also play a role.

As a result, physicians without a particular interest in photodermatology may only occasionally see and report cases of drug-induced photosensitivity.¹⁰ Due to underreporting as well as the diversity and abundance of drugs with photosensitizing potential, there are only rough approximations as to the actual incidence of photosensitive reactions. In a report by Chaabane *et al.*¹⁹ on patients presenting with drug-induced skin adverse reactions, photosensitivity was the third commonest cause. In specialized photodiagnostic units, systemic drug-induced photosensitivity is reported to account for up to 15% of photodermatoses.^{20–25} However, these cases only represent those actually referred for investigation of suspected photosensitivity and as such do not reflect the true incidence.¹⁰

Up to the present, a large quantity of drugs has been associated with photosensitivity and this number is increasing constantly.⁸ As part of our analysis, we have identified 387 drugs with photosensitivity reported in the literature or in drug databases. To our knowledge, this is the largest compilation of potentially photosensitive drugs published so far. Of note, only 75.2% out of these agents were effectively prescribed in DE and 56.9% in AT, respectively. These data also suggest that, even if there are some disparities between nations, a large part of pharmaceuticals available for prescription might be comparable among European countries.

When further analysing the dispensed drugs, it becomes evident that only a minority of all dispensed agents have a photosensitizing potential. However, when looking at the percentage of photosensitizers of all dispensed drugs, a completely different picture evolves. Out of all drug dispensings, the mean cumulative proportion of photosensitive drugs was 49.5% in DE and 48.2% in AT, respectively. These data indicate that although the number of photosensitizers accounts for only a small portion of all drugs available, almost half of all drug dispensings contained a potentially photosensitive pharmaceutical agent. The importance of photosensitizing drugs is further underlined by the fact that the number of their dispensings was increasing during the study period, even if a plateau phase (or even decrease) was observed over the more recent years.

Assuming that the incidence of photosensitive adverse reactions is determined by the frequency of its use and its photosensitizing potential a correlation of these two parameters was performed. The resulting scatter plot was subdivided into four segments revealing two segments that contain compounds with a higher probability for causing cutaneous photosensitivity reactions. The segment 'X2' contains drugs with a low number of prescriptions but a high photosensitizing potential, such as vemurafenib, or amiodarone. Given their rather narrow indications with limited total prescriptions in combination with their well-known photosensitizing potential, the number of cases of photosensitivity due to these drugs is expected to be rather low. The segment 'X3' represents the segment with both a well-documented photosensitizing potential and a high prescription rate. In DE, only two agents fall into this category, hydrochlorothiazide and ibuprofen. In AT, none of the drugs falls into this category but several drugs are close to it including hydrochlorothiazide, furosemide, ciprofloxacin, naproxen and ibuprofen. Generally, compounds in the 'X3' segment represent those drugs being most important from a public health perspective as they will account for most (and potentially undiagnosed) cases of photosensitivity.

The category 'X3' becomes even more important when considering the potential long-term effects of photosensitizing drugs. Besides acute cutaneous adverse effects, an increasing number of reports also suggest chronic sequelae such as increased photoaging or photocarcinogenesis.²⁶ While there is overwhelming evidence for the photocarcinogenic effects of psoralens,^{25–32} several

other phototoxic drugs have been associated with photocarcinogenesis.^{33–38} This includes fluoroquinolones^{36,38–42} such as ciprofloxacin or lomefloxacin, NSAIDs,³⁶ thiazide diuretics,^{34,35,37,43} amiloride,³⁴ amiodarone,^{44–47} tetracyclines,³⁴ azathioprine,^{48–51} vemurafenib^{52–54} or voriconazole.⁵⁵ In general, these drugs may increase the risk for spinocellular carcinoma and melanoma although there are also reports on an increased risk for basal cell carcinoma with amiodarone, ciprofloxacin or tetracycline.^{34,43–46} However, this aspect remains to be fully elucidated as some drugs such as NSAIDs that may induce photosensitivity can even prevent photocarcinogenesis.⁵⁶ Moreover, epidemiological data do not unequivocally support the association between drug-induced photosensitivity and an elevated risk of skin cancer; instead, there are also data on reduced risk.³³ The complexity of this topic is further exemplified by the different mechanisms involved in drug-induced photosensitivity. Besides the classical mechanism via exogenous chromophores and absorption, some drugs induce photosensitivity by affecting DNA repair (e.g. in case of PARP inhibitors⁵⁷), by interacting with a signalling pathway (e.g. in case of protein kinase inhibitors⁵⁸) or by DNA adducts and interstrand cross-linking (e.g. in case of psoralens^{5,59}). These diverse mechanisms of photosensitivity do not only complicate our understanding, they also explain why drug-induced photosensitivity does not automatically correlate with photocarcinogenicity. However, the issue of drug-induced photocarcinogenicity was beyond the scope of the current investigation.

A main limitation of the present study is the fact that it did not include over-the-counter drugs and drugs dispensed to patients without public insurance coverage. In addition, drugs with a price below the copayment rate were also not factored in the analysis since their dispensing is not registered by the statutory health insurances. In the end, it would be desirable to determine the actual number of individuals which were exposed to the photosensitive risk. However, from an epidemiological point of view, an extrapolation from the number of dispensed photosensitive drugs to the number of individuals affected is not possible. From the available data set, it is not possible to determine how many packages of the individual drugs were prescribed for how many patients and whether these medications were actually taken by these individuals (and for how long). These questions could only be clarified satisfactorily within the context of a prospective patient-centred study. In addition, the ‘indicator’ of the photosensitizing potential of a drug as established in our study only reflects current published knowledge on drug-induced photosensitivity. Unpublished cases or cases not published in MEDLINE or in Litt’s Drug Eruption & Reaction Database were not captured by the current analysis.

In summary, our findings indicate that photosensitive drugs represent about half of all dispensings of reimbursed drugs in DE and AT. Besides the potential of causing acute cutaneous photosensitivity reactions, the recent reports on the association of phototoxic drugs with photocarcinogenesis cause particular

concern. In the latter regard, special attention should be given to drugs with high dispensing numbers and a high phototoxic potential, such as hydrochlorothiazide.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Analysis of the distribution of photosensitizing drug dispensings according to drug classes.

Figure S2. Analysis of the references on photosensitivity.

Table S1. Compilation of reports on photosensitivity per pharmaceutical compound based on a MEDLINE literature search ($n = 1697$).

Appendix S1. Methods.