Systemic drug photosensitivity—Culprits, impact and investigation in 122 patients

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Abstract
Background: Systemic drugs are a potentially reversible cause of photosensitivity. We explore prevalence, impact, phototest findings and culprit drugs.

Methods: Retrospective review of patients was diagnosed with drug-induced photosensitivity in a specialist photoinvestigation centre (2000-2016), using data recorded in standardized pro forma. Patients underwent detailed clinical evaluation. Monochromator phototesting was performed to 300 ± 5 nm, 320 ± 10 nm, 330 ± 10 nm, 350 ± 20 nm, 370 ± 20 nm, 400 ± 20 nm, 500 ± 20 nm and 600 ± 20 nm. Broadband UVA and solar-simulated radiation (SSR) testing were performed, and photopatch testing and laboratory tests examined for other causes of photosensitivity. DLQI was evaluated.

Results: Prevalence of drug-induced photosensitivity was 5.4% (122/2243) patients presenting with photosensitivity. Patients with drug-induced photosensitivity were 52.5% female; median 62 years (range 11-86); phototype I (17.2%), II (39.3%), III (26.2%), IV (6.5%), V (4.1%). Fifty-five (45.1%) patients had reduced erythemal thresholds on monochromator phototesting: 83.6% to UVA alone, 14.5% to both UVA and UVB, 1.8% to UVA and visible light; 61.4% (n = 75) showed abnormal response to broadband UVR. Drugs implicated: quinine (11.5%), diuretics (10.7%; thiazide 9.8%), antifungals (9.8%), proton-pump-inhibitors (9.8%), angiotensin-converting enzyme inhibitors (7.4%), anti-inflammatory drugs (6.6%), statins (5.7%), selective serotonin reuptake inhibitors (4.9%), calcium channel antagonists (3.3%), anti-epileptics (3.3%), tricyclic antidepressants (3.3%), beta-blockers (2.5%), antibiotics (2.5%), others (≤1.6% cases each). Emerging culprits included azathioprine (2.5%) and biologics (TNF-α inhibitors, denosumab; 2.5%). Median DLQI was 11 (range 2-27) for the past year.

Conclusion: Classically described photosensitizing drugs such as thiazides and quinine remain common offenders, while emerging culprits include biologics such as TNF-α inhibitors and proton-pump-inhibitors. There is very large impact on life quality; identification facilitates measures including drug cessation and implementation of appropriate photoprotection.
1 | INTRODUCTION

Drug-induced photosensitivity is an important, potentially reversible cause of photosensitivity, and is a potential adverse effect of many medications. While systematic reviews have explored the range of medications causing photosensitivity, the prevalence of these drug reactions is largely unknown. A retrospective analysis of reports suggested drug-induced photosensitivity may account for up to 8% of cutaneous adverse effects from drugs. However, estimates of prevalence are likely to be an underestimate as many cases may be undiagnosed or unreported. Studies are largely based on clinical observation, including case series and case reports, with a minority incorporating phototesting. Objective evidence is therefore usually lacking. Moreover, culprit drugs and the expression of drug-induced photosensitivity alter as new drugs emerge. Thus, more awareness is required regarding current culprits, diagnosis and impact on patients.

Mechanisms of drug-induced photosensitivity include phototoxicity, photoallergic reactions and drug-induced lupus erythematosus (LE), with most cases of systemic drug-induced photosensitivity thought to be exerted through phototoxicity. Pathogenesis of phototoxic reactions is secondary to activation of the photosensitizing drug or its metabolite(s) by ultraviolet radiation (UVR) which can then lead to photosensitivity either through direct cellular or oxidative and free radical damage. Phototoxicity may theoretically occur in any individual exposed to enough of the drug or relevant wavelength of UVR, although the threshold differs across individuals. Photoallergic reactions to systemic drugs are less common, more often occurring due to topical agents. They are mediated by cell-mediated type IV hypersensitivity responses and require sensitization to the offending drug. With topical though not systemic photoallergy, photopatch testing is usually very useful in determining the causative agents.

Patients with drug-induced photosensitivity can be investigated at a photodiagnostic unit, where their features of photosensitivity are differentiated from those of other photodermatoses. A detailed clinical appraisal is required to explore for culprit drugs, including timing of onset of symptoms and of medication. Clinical features may include burning, itching and a rash affecting sun-exposed sites; this is most often either with a pronounced sunburn-like reaction or with an eczematous rash, while other features including photo-onycholysis, LE and lichenoid reactions occur more rarely. Monochromator phototesting to examine erythemal thresholds to narrowband UVB, UVA and visible radiation helps objectively identify presence of photosensitivity and its action spectrum. Resolution of abnormal responses on retesting or clinical improvement after a several month period of drug cessation can assist confirmation of drug-induced photosensitivity.

Our objectives were to explore the prevalence, impact, current and emerging culprits of drug-induced photosensitivity, in patients with features of photosensitivity investigated at a photodiagnostic unit.

2 | METHODS

2.1 | Patients and methodology

This was a case series of patients diagnosed with drug-induced photosensitivity over a 16-year period (Jan 2000-Jan 2016) in a specialist clinical photoinvestigation centre (Photobiology Unit, Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester, UK). Patients are referred, mainly by general dermatologists, from a wide geographic area of Northern and Central England and Wales, UK. Data were obtained with standardized pro forma and phototest methods. Detailed clinical history was taken from patients with timelines of medications taken and symptoms of photosensitivity and they were examined for signs of a photodistributed rash and its morphology. Detailed monochromator phototesting was performed to narrow bandwidths of UVR and visible radiation from 300 to 600 nm. Additionally, patients underwent broadband phototesting with low-dose UVR on up to 3 consecutive days in accordance with the unit’s routine photo-provocation schedule. Photopatch with control patch testing was performed to sunscreen filters and non-steroidal-anti-inflammatory drugs (NSAIDs), along with laboratory tests including connective tissue disease (CTD) screen, urine and blood porphyrin testing and serum 25-hydroxyvitamin-D (25OHD) level. Dermatology Life Quality Index (DLQI) was evaluated, with scores for the past week and the past year.

2.2 | History and examination pro forma

Detailed history and examination were taken using a standardized pro forma to include: age and season at onset; number of episodes per year; whether rash is continuous or present/absent/less severe in winter; any increased tolerance as summer progresses; precipitants of rash; use of sunscreens and whether use helps prevent rash; whether rash can be provoked through window glass; duration of sun exposure needed to provoke rash; duration between exposure to sun and appearance of rash; duration of lesions; symptoms of condition; drug history at the onset of photosensitivity with start and stop dates; present systemic drugs and topical agents with start and stop dates; any significant consumption of food/drink containing psoralens or quinine; previous treatments for the rash including dates; past medical history; family history; phototype; occupation/outdoor activities; effect on quality of life (including restriction in outdoor activity). Examination of rash and available photographs was performed to evaluate morphology and distribution.
2.3 | Photoinvestigation

2.3.1 | Monochromator phototesting

Phototesting against narrow bandwidths of UVB, UVA and visible radiation was performed on the central/upper back to determine the minimal erythemal dose (MED) and define the action spectrum. Patients were exposed to 300, 320, 330, 350, 370, 400, 500 and 600 nm (half-maximum bandwidth 5 nm at 300 nm, 10 nm at 320 and 330 nm; 20 nm at all other wavelengths) using a xenon arc lamp (1 KW short arc, Newport Spectra-Physics Ltd, Didcot, UK) coupled to a 1/4m grating monochromator (Newport Spectra-Physics Ltd) (Table 1). Irradiance was measured using a calibrated thermopile (Medical Physics, Dryburn Hospital, Durham, UK) and digital voltmeter (Medical Physics, Royal Liverpool University Hospital, Liverpool, UK). Patients were exposed on their back to a geometric progression of doses (common ratio = \(\sqrt{2}\)) at each wavelength. The lowest dose at which a visible erythemal reaction was induced, that is the MED, was noted at 24 hours.7

2.3.2 | Broadband UVR provocation testing

Testing was performed on 5 × 5 cm areas of skin of the ventral forearm. All patients were given 15 J/cm\(^2\) broadband UVA (320-400 nm) using a custom-built arm exposure unit incorporating Cleo Performance™ bulbs (Phillips Healthcare UK Ltd. Guildford UK). Additionally from 2009 onwards, provocation testing was performed on the contralateral forearm using 10J/cm\(^2\) solar-simulated radiation (SSR) (290-400 nm, 1 KW xenon arc plus atmospheric attenuation filter Newport Spectra-Physics Ltd).7

2.3.3 | Photopatch testing

This was carried out on the lower back to examine for presence or co-existence of photocontact allergy. From 2009, this involved 24 agents: 19 UV filters, 5 NSAIDs (Chemotechnique Diagnostics, Vellinge, Sweden)\(^8\) and sunscreen products including patients’ own, while prior to 2009, the photopatch series comprised 10 agents: 9 organic UV filters and sunscreen products. Duplicate patches were applied (day 1) to skin of the mid-back for 24 hours following which one set was irradiated (day 2) with broadband UVA (5J/cm\(^2\); reduced dose where low erythemal thresholds) (320-400 nm; UVAL 801, Herbert Waldmann GmbH & Co. KG, Villingen-Schwenningen, Germany). Visual readings were taken at 24 and 48 hours post-UVR (days 3, 4) to examine for a response, using the International Contact Dermatitis Research Group (ICDRG) grading.7,9

2.4 | Laboratory tests

These included CTD screen, urine and blood porphyrin testing, and serum 25OHD level.

2.5 | Quality of life evaluation

The DLQI is a questionnaire used to assess the quality of life (QoL) which has been validated in dermatology conditions, although not specifically for photosensitivity conditions.6 The DLQI was completed at the time of photoinvestigation by patients from January 2011 onwards, to assess the impact of drug-induced photosensitivity on QoL both in the past week and past year to take into account seasonal variation.

3 | RESULTS

3.1 | Patient demographics

A total of 2243 patients underwent investigation including phototesting in the photobiology unit from January 2000 to January 2016. Of these, 122 patients were diagnosed with drug-induced photosensitivity, giving a prevalence of 5.4% within this population. Of the 122 patients, 64 were female (52.5%). Median age was 62, with range 11 to 86 years.

### TABLE 1

| Wavelength, nm \(^a\) | Dose series (J/cm\(^2\)) |
|-----------------------|--------------------------|
| 300 (5)               | 0.0018 0.0025 0.0035 0.005 0.007 0.01 0.014 0.02 0.028 0.04 0.08 |
| 320 (10)              | 0.13 0.18 0.25 0.35 0.5 0.7 1.0 1.4 2.0 2.5 4.0 |
| 330 (10)              | 0.31 0.44 0.63 0.90 1.3 1.8 2.5 3.5 5.0 7.0 10 14 |
| 350 (20)              | 0.63 0.90 1.3 1.8 2.5 3.5 5.0 7.0 10 14 20 25 40 |
| 370 (20)              | 1.8 3.5 7.0 14 20 28 57 |
| 400 (20)              | 3.5 7.0 14 28 40 57 113 |
| 500 (20)              | 50 |
| 600 (20)              | 50 |

\(^a\) Extended lower dose ranges are used when thresholds are lower than the doses shown.

\(^b\) Full-width half-maximum bandwidth in parentheses.
frequencies of patients’ Fitzpatrick skin types were as follows: I (17.2%), II (39.3%), III (26.2%), IV (6.5%), V (4.1%), VI (0%); not recorded (6.7%).

3.2 | Clinical features

The clinical features presented by patients are shown in relation to their suspected culprit drug (Table 2). The median duration of symptoms was 3 years. While 53.3% of patients reported symptoms occurring mainly in spring-summer months, 37.7% reported symptoms all year round. The majority, 58%, showed features of a phototoxic reaction, that is sunburn-like in appearance. Patients typically reported experiencing a burning erythema with quick onset following sun exposure and accompanying oedema in severe reactions. A substantial minority, 32%, showed predominantly eczematous features, with skin dryness and scaling. Other clinical presentations were occasionally seen, notably including lichenoid reactions relating to quinine and pseudoporphyria with naproxen. A patient taking clesuvelam had an immediate wheal and flare response to phototesting, consistent with drug-induced solar urticaria. Some patients with pre-existing polymorphic light eruption (PLE) reported exacerbation of this condition since onset of the culprit drug. A proportion of patients showing acute phototoxicity to voriconazole (n = 11) also showed features of chronic photodamage. This included patients with cheilitis (5/11) and multiple lentigines (2/11). One patient on voriconazole had also developed a squamous cell carcinoma (SCC) on the ear while on voriconazole, with a further SCC 5 years after stopping voriconazole. We refer to our previous review for further information on the clinical characteristics and implications of voriconazole photosensitivity.10

3.3 | Phototesting

3.3.1 | Monochromator phototesting

Patient phototesting results are shown in relation to their culprit drug in Table 3. Overall, 45.1% (n = 55) of patients had reduced (abnormal) MED on monochromator phototesting: 83.6% (n = 46) showed reduced MED to monochromator testing with UVA (320-400nm), 14.5% (n = 8) to UVA plus UVB (300-400 nm) and 1.8% (n = 1) to UVA plus visible light (320-500nm). In patients with UVA sensitivity and accompanying UVB and/or visible light sensitivity, MED was reduced to a greater degree in the UVA than UVB or visible light regions. Nineteen (15.6%) of the 122 patients were phototested after the photoactive drug had been discontinued. The frequency of reduced MED seen at each wavelength on monochromator phototesting in patients diagnosed with drug-induced photosensitivity is shown in Figure 1.

3.3.2 | Broadband phototesting

91.8% (n = 112/122) of patients showed a response to broadband UVR; these included 30.3% (n = 37) showing mild erythema only. It is possible that mild erythema can occur on multiple provocation testing even with a UVR dose that is suberythemal when applied once. Therefore, mild erythemal responses were not considered to be pathological. 61.5% (n = 75) of patients had abnormal responses comprising moderate-severe erythema. A minority of patients showed an eczematous clinical appearance (scaling, tiny papules) when reviewed at 24 hours after the 2nd or 3rd provocation. 52.5% (n = 64/122) of patients had abnormal responses to broadband UVA, and 57.0% (n = 53/93) of patients who had SSR provocation performed had abnormal responses. In patients who had both SSR and broadband UVA phototesting performed, 15.1% (n = 14) had abnormal reactions with one source only (SSR only n = 11; broadband UVA only n = 4). Thus, SSR testing was particularly successful, while there was additional benefit from performing both.

3.3.3 | Photopatch testing

Positive photopatch testing to one or more agents with negative control patch testing was seen in 6 of the 122 patients. Agents were ketoprofen 1% (n = 2), butylmethoxydibenzoylmethane/avobenzone (n = 2) and benzophenone-3/oxybenzone (n = 3). In one patient who had a positive photopatch test to benzophenone-3, a relevant previous reaction to sunscreen was reported by the patient and sunscreen photocontact allergy concurrent with the systemic drug photosensitivity was clinically suspected. Additionally, 11 patients showed positive patch testing alone; agents were homosalate, methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M), benzophenone-3, octylmethoxy-cinnamate, benzophenone-4 and patients’ own sunscreen products. These findings were unrelated to the patients’ systemic drug photosensitivity and patients were advised to avoid products containing these compounds.

3.4 | Laboratory testing

Porphyrin plasma and urine test were positive in 2 of 117 patients. These results were weakly positive urine porphyrin: creatinine ratio in one patient and weakly positive plasma porphyrin peak at 622nm in another patient, which were not considered relevant. Antinuclear antibody (ANA) tests were positive in 15 of 115 patients. Most (n = 13) had weakly positive ANA titres between 1:20 and 1:100 which were not considered clinically relevant; their clinical features were in keeping with phototoxicity (burning, erythema). The remaining two patients had ANA titres of 1:1000, but again no clinical features suggestive of LE. One showed severe UVA sensitivity to quinine, with phototoxic clinical features; her symptoms and phototest findings resolved on discontinuation of quinine. The remaining patient’s reaction was atypical, with clinical features consistent with pseudoporphyria in relation to naproxen treatment of rheumatoid arthritis; histology showed non-specific erosions.

Positive anti-double-stranded DNA (anti-dsDNA; 86 iu/ml; reference range > 10 iu/mL) was found in a patient photosensitive to mesalazine, who had reduced MED to UVA and UVB; clinically, the features fitted better with phototoxicity than drug-induced LE.
| Drug class                | Suspected culprit drug | Total n\(^a\) | Sunburn-like n\(^a\) | Eczematous n\(^a\) | Other n\(^a\) |
|--------------------------|------------------------|---------------|----------------------|-------------------|--------------|
| Antimalarials            | Quinine               | 14            | 2                    | 8                 | Lichenoid 4  |
|                         | Hydroxychloroquine    | 1             |                      |                   |              |
| Thiazide diuretics       | Bendroflumethiazide   | 10            | 4                    | 6                 |              |
|                         | Hydrochlorothiazide   | 1             | 1                    |                   |              |
|                         | Indapamide            | 1             | 1                    |                   |              |
| Antifungals              | Voriconazole          | 11            | 11                   |                   | Cheilitis 5  |
|                         | Terbinafine           | 1             | 1                    |                   | Lentigines 2 |
| Proton-pump inhibitors   | Omeprazole\(^b\)      | 8             | 4                    | 4                 |              |
|                         | Lansoprazole\(^b\)    | 3             | 2                    | 1                 |              |
|                         | Rabeprazole\(^b\)     | 1             |                      |                   | PLE exacerbated 1 |
| Angiotensin-converting enzyme inhibitors | Lisinopril\(^b\) | 2             | 2                    |                   |              |
|                         | Enalapril             | 3             | 1                    | 2                 |              |
| Anti-inflammatory         | Naproxen              | 2             | 1                    |                   | Pseudoporphyia 1 |
|                         | Ibuprofen             | 2             | 1                    | 1                 |              |
|                         | Mefenamic acid        | 1             | 1                    |                   |              |
|                         | Sulphasalazine        | 1             | 1                    |                   |              |
|                         | Mesalazine            | 2             | 2                    |                   |              |
| Statins                  | Simvastatin           | 5             | 1                    | 4                 |              |
|                         | Atorvastatin          | 2             | 1                    | 1                 |              |
| Selective serotonin reuptake inhibitors | Fluoxetine            | 4             | 2                    | 1                 | Solar urticaria 1 |
|                         | Sertraline            | 2             | 2                    |                   |              |
| Calcium channel antagonists | Amlodipine           | 3             | 1                    | 2                 |              |
|                         | Diltiazem             | 1             | 1                    |                   |              |
| Anti-epileptics          | Carbamazepine         | 2             | 1                    |                   | LE 1         |
|                         | Lamotrigine\(^b\)     | 1             | 1                    |                   |              |
|                         | Phenobarbitone\(^b\)  | 1             | 1                    |                   |              |
| Tricyclic antidepressants | Amitriptyline        | 2             | 1                    |                   | PLE exacerbated 1 |
|                         | Nortriptyline         | 2             | 2                    |                   |              |
| β-blockers               | Bisoprolol\(^b\)      | 1             |                      |                   | PLE exacerbated 1 |
|                         | Atenolol\(^b\)        | 2             | 2                    |                   |              |
| Antibiotics              | Tetracyclines         | 1             | 1                    |                   |              |
|                         | Ciprofloxacin         | 1             | 1                    |                   |              |
|                         | Dapsone               | 1             | 1                    |                   |              |
| Immunosuppressants       | Azathioprine          | 3             | 3                    |                   |              |
| Biologics                | Etanercept\(^b\)      | 1             | 1                    |                   |              |
|                         | Infliximab\(^b\)      | 1             | 1                    |                   |              |
|                         | Denosumab\(^b\)       | 1             | 1                    |                   |              |
| Angiotensin-II-receptor antagonists | Candesartan    | 2             | 1                    | 1                 |              |
| Retinoids                | Isotretinoin          | 2             | 2                    |                   |              |
| Loop diuretics           | Bumetanide            | 1             |                      |                   | PLE exacerbated 1 |
| Antiarrhythmic agents    | Clopidogrel           | 1             | 1                    |                   |              |

(Continues)
Symptoms resolved on cessation of mesalazine, with normalization of MED. A further patient had positive anti-dsDNA (71 iu/mL), but this was pre-existing in relation to chilblain lupus.

Extractable nuclear antigen (anti-Ro/SSA) was positive in one patient with severe UVA sensitivity, who was felt to have drug-induced LE. Clinical features were severe erythema and oedema affecting sun-exposed sites and were replicated on provocation testing. The patient was taking methyldopa, which is associated with drug-induced LE. However, the onset of symptoms was closely associated with commencement of carbamazepine, which has also been linked to drug-induced LE in case reports, and this was concluded to be the more likely culprit. Anti-La/SSB antibodies were slightly elevated (1.5 U; reference range > 1.0 U) in a patient on voriconazole and considered non-relevant, the patient showing features of a phototoxic reaction.

Serum 25OHD levels were performed in 68 patients: 61.1% had low 25OHD levels: 35.2% (n = 24) were insufficient (25-50 nmol/L) and 25.0% (n = 17) were deficient (<25 nmol/L).

### 3.5 Culprit drugs

Suspect drugs are shown (Tables 2 and 3). The drugs comprised both those well known to cause photosensitivity and emerging culprits with little information currently in the literature regarding photosensitivity reactions.

Emerging culprits noted from 2009 onwards, included azathioprine and biologics, that is TNF-α-inhibitors and the anti-RANKL agent, denosumab. Denosumab-induced UVA photosensitivity (350 and 370 nm) was seen in an 86-year-old woman, skin type II, with a background of rheumatoid arthritis. There was one case of etanercept-induced severe photosensitivity to UVA in a 33-year-old woman, skin type II; ANA was mildly positive (1:100 homogenous) but skin biopsy with immunofluorescence did not show evidence of LE. Although on etanercept for several years, cessation of etanercept led to significant clinical improvement of photosensitivity after 6 months with normalization of MED on monochromator phototesting.

A 21-year-old man presented with photosensitivity chronologically linked to infliximab. Although stopping infliximab modestly improved his photosensitivity symptoms, his photosensitivity continued. The patient was taking concomitant azathioprine, and at 8 months following cessation of the azathioprine, there was significant improvement in his photosensitivity, with near normalization of his MED at 300-400 nm (UVB + UVA), suggesting possible synergistic effect of azathioprine photosensitivity with infliximab.

Azathioprine-induced photosensitivity was also seen in an 11-year-old girl with skin type II. Monochromator phototesting revealed reduced MED to UVA (320-370 nm) wavelengths. Two further cases of azathioprine-induced photosensitivity were seen: a 25-year-old woman, skin type II, exhibiting UVA sensitivity at 370 nm, and a 53-year-old man, skin type II, with abnormal response to broadband UVA and SSR.

In 8 patients overall, it was possible that a further drug may have been contributing to the drug photosensitivity; culprit drug/potential further culprit: infliximab/azathioprine (n = 1), naproxen/bendroflumethiazide (n = 1), ciprofloxacin/ramipril (n = 1), atenolol/diltiazem (n = 1), ibuprofen/quinine (n = 1), amitriptyline/bendroflumethiazide (n = 1), ramipril/diltiazem (n = 1), atorvastatin/omeprazole (n = 1). [Correction added on 14 July 2020, after first online publication: In table 2, `TASHGold injection' has been corrected to ‘Gold Injection’ in this version.]

### 3.6 Follow-up and repeat phototesting

Once a culprit drug was suspected through detailed history taking and phototesting, patients were advised to stop and substitute this
| Drug class          | Drug               | n  | % patients | Broadband phototesting [n abnormal] | Monochromator phototesting [n with reduced MED] |
|---------------------|--------------------|----|------------|----------------------------------|---------------------------------------------|
|                     |                    |    |            | UVAa                            | UVBa, UVAa, VLa                             |
| Antimalarials       | Quinine           | 14 | 12.3%      | + [12]                          | + [1]                                      |
|                     | Hydroxychloroquine| 1  | -          | + [1]                           | -                                          |
| Thiazide diuretics  | Benfloflumethiazide| 10 | 9.8%       | + [5]                           | -                                          |
|                     | Hydrochlorothiazide| 1  | + [1]      | + [1]                           | -                                          |
|                     | Indapamide         | 1  | + [1]      | + [1]                           | -                                          |
| Antifungals         | Voriconazole       | 11 | 9.8%       | + [2]                           | -                                          |
|                     | Terbinafine        | 1  | -          | np                             | -                                          |
| Proton-pump inhibitors | Omeprazole       | 8  | 9.8%       | + [6]                           | + [1]                                      |
|                     | Lansoprazole       | 3  | + [1]      | + [1]                           | + [1]                                      |
|                     | Rabeprazole        | 1  | + [1]      | (+) [1]                         | -                                          |
| Angiotensin-converting enzyme inhibitors | Lisinopril | 2  | 7.4%       | + [2]                           | -                                          |
|                     | Enalapril          | 3  | + [1]      | + [1]                           | + [1]                                      |
|                     | Ramipril<sup>b</sup> | 4  | + [3]      | + [1]                           | + [1]                                      |
| Anti-inflammatory   | Naproxen<sup>b</sup> | 2  | 6.6%       | + [1]                           | -                                          |
|                     | Ibuprofen<sup>b</sup> | 2  | (+) [1]    | (+) [1]                         | -                                          |
|                     | Mefenamic Acid     | 1  | + [1]      | + [1]                           | + [1]                                      |
|                     | Sulphasalazine     | 1  | + [1]      | np                             | -                                          |
|                     | Mesalazine         | 2  | + [2]      | + [1]                           | + [1]                                      |
| Statins             | Simvastatin        | 5  | 5.7%       | + [1]                           | -                                          |
|                     | Atorvastatin<sup>b</sup> | 2  | (+) [2]    | + [1]                           | -                                          |
| Selective serotonin reuptake inhibitors | Fluoxetine | 4  | 4.9%       | + [2]                           | -                                          |
|                     | Sertraline         | 2  | + [1]      | + [1]                           | + [1]                                      |
| Calcium channel antagonists | Amlodipine | 3  | 3.3%       | + [2]                           | -                                          |
|                     | Diltiazem          | 1  | -          | (+) [1]                         | + [1]                                      |
| Anti-epileptics     | Carbamazepine      | 2  | 3.3%       | (+) [1]                         | -                                          |
|                     | Lamotrigine        | 1  | + [1]      | + [1]                           | -                                          |
|                     | Phentobarbitone    | 1  | -          | (+) [1]                         | + [1]                                      |
| Tricyclic antidepressants | Amitripyline<sup>b</sup> | 2  | 3.3%       | -                               | -                                          |
|                     | Nortriptyline      | 2  | -          | -                               | -                                          |

(Continues)
**TABLE 3** (Continued)

| Drug class               | Drug                  | n  | % patients | Broadband phototesting [n abnormal] | Monochromator phototesting [n with reduced MED] |
|--------------------------|-----------------------|----|------------|-------------------------------------|-----------------------------------------------|
|                          |                       |    | UVA        | SSR                                 | UVB | UVA | VL  |
| β-Blockers               | Bisoprolol            | 1  | 2.5%       | + [1]                               | -   | + [1] | -   |
|                          | Atenolol\(^b\)        | 2  |            | + [2]                                | np  |      | +[1] |
| Antibiotics              | Tetracyclines         | 1  | 2.5%       | -                                   | -   | -   | -   |
|                          | Ciprofloxacin\(^b\)   | 1  |            | + [1]                               | -   | -   | -   |
|                          | Dapsone               | 1  |            | + [1]                               | -   | + [1] | -   |
| Immunosuppressants       | Azathioprine          | 3  | 2.5%       | + [2]                               | -   | + [2] | -   |
| Biologics                | Etanercept            | 1  | 2.5%       | + [1]                               | -   | + [1] | -   |
|                          | Infliximab\(^b\)      | 1  |            | + [1]                               | + [1] | + [1] | -   |
|                          | Denosumab             | 1  | (+) [1]    | + [1]                               | -   | + [1] | -   |
| Angiotensin-II-receptor  | Candesartan           | 2  | 1.6%       | (+) [1]                             | +[1] |      | -   |
| antagonists              |                       |    |            |                                     |     |     |     |
| Retinoids                | Isotretinoin          | 2  | 1.6%       | + [2]                               | -   | + [2] | -   |
| Loop diuretics           | Bumetanide            | 1  | 0.8%       | -                                   | -   | -   | -   |
| Antiarrhythmic agents    | Amiodarone            | 1  | 0.8%       | + [1]                               | np  | -   | -   |
| Antiplatelet agents      | Clopidogrel           | 1  | 0.8%       | + [1]                               | + [1] | -   | -   |
| Other                    | Allopurinol           | 1  | 8.2%       | + [1]                               | -   | -   | -   |
|                          | Colesevelam           | 1  |            | + [1]                               | + [1] | -   | -   |
|                          | Gold injection        | 1  |            | + [1]                               | + [1] | -   | -   |
|                          | Levothyroxine         | 1  |            | (+) [1]                             | (+) [1] | -   | -   |
|                          | Metformin             | 1  |            | + [1]                               | (+) [1] | -   | -   |
|                          | Nicorandil            | 1  |            | (+) [1]                             | (+) [1] | -   | -   |
|                          | Parthenolide          | 1  |            | (+) [1]                             | (+) [1] | -   | -   |
|                          | Tamoxifen             | 1  |            | (+) [1]                             | np  | -   | -   |
|                          | Tamsulosin            | 1  |            | (+) [1]                             | (+) [1] | -   | -   |
|                          | Vitamin B12           | 1  |            | + [1]                               | -   | -   | + [1] |

\(^a\)np, not performed; + denotes abnormal response on broadband provocation testing/reduced MED on monochromator testing; (+) denotes mild erythema response on broadband provocation testing.

\(^b\)Patients where a further drug may be contributing to the drug photosensitivity; drug listed above/possible contributing drug: infliximab/azathioprine (n = 1), naproxen/bendroflumethiazide (n = 1), ciprofloxacin/ramipril (n = 1), atenolol/diltiazem (n = 1), ibuprofen/quinine (n = 1), amitriptyline/bendroflumethiazide (n = 1), ramipril/diltiazem (n = 1), atorvastatin/omeprazole (n = 1).
drug if able with guidance of their relevant specialist or general practitioner. In addition, patients were advised on detailed photoprotection measures, including suitable clothing and hats, the use of high UVA protection and sun protection factor (SPF) sunscreens and UVR blocking window films for car, office and home. Vitamin D supplementation of 800 IU daily was recommended in the case of vitamin D deficiency or insufficiency.

Sixty patients re-attended the photobiology unit, the majority reporting complete resolution of symptoms after cessation of the culprit drug, while 14 reported persistent symptoms. Of the latter, 3 patients were unable to stop the suspect drugs (omeprazole, ciprofloxacin/ramipril, lansoprazole) for medical reasons. A further patient (on bendroflumethiazide), was diagnosed to have photoaggravated eczema. Of the remaining ten patients, photosensitivity resolution was clinically incomplete (suspect drugs: simvastatin n = 2, lansoprazole n = 1, omeprazole n = 1, quinine n = 2, fluoxetine n = 1, sulphasalazine n = 1). Additionally, phototesting remained abnormal in the patient taking ciprofloxacin/ramipril who was unable to stop these drugs.

Repeat phototesting was performed in 26 of the 60 patients. This confirmed resolution of photosensitivity in 18 patients following cessation of the suspect drug (bumetanide n = 1, bendroflumethiazide n = 1, quinine n = 5, lisinopril n = 1, allopurinol n = 1, atenolol n = 1, etanercept n = 1, naproxen n = 1, isotretinoin n = 1, mesalazine n = 1, sertraline n = 1, omeprazole n = 1, colesvealam n = 1, infliximab n = 1). Incomplete or lack of resolution of abnormal phototest results was seen in 7 patients following drug cessation (simvastatin n = 1, lansoprazole n = 1, omeprazole n = 1, quinine n = 2, fluoxetine n = 1, sulphasalazine n = 1).

### 3.7 Dermatology life quality index

The DLQI questionnaire, introduced routinely in 2011, was completed by 58 patients at the time of photoinvestigation (Table 4). A higher impact was seen for the past year than the past week, with many patients visiting the photoinvestigation unit in winter time. Median DLQI score was 6 (range 0-29) for the past week and 11 (range 2-27) for the past year.

| No. of patients (%) | DLQI band         |
|---------------------|-------------------|
| 1 (2%)              | 0-1 (no effect)   |
| 4 (7%)              | 2-5 (small effect)|
| 23 (40%)            | 6-10 (moderate effect) |
| 19 (32%)            | 11-20 (very large effect) |
| 11 (19%)            | 21-30 (extremely large effect) |

Drug-induced photosensitivity is an important potentially reversible cause of photosensitivity, with 5.4% of patients undergoing photoinvestigation in our unit between 2000 and 2016 showing photosensitivity attributable to this. Within other specialist photoinvestigation units, drug-induced photosensitivity has been reported to account for between 2% and 15% of photodermatoses diagnosed, including 4% in the Scottish Photobiology service. It is likely that this is the tip of the iceberg, as many drugs have the potential to photosensitize, whereas only selected patients will achieve referral to scarce tertiary diagnostic units.

Our review shows that the previously reported common photosensitizing drugs remain top of the list, in particular quinine and thiazide diuretics, responsible for 11.5% and 9.8% of cases of drug-induced photosensitivity, respectively. A high percentage of patients with voriconazole-induced photosensitivity (9%) was observed, attributable to our close geographic links with the UK National Aspergillosis Centre, while reactions to proton-pump inhibitors (PPI) were also prevalent (9.8%).
Overall, findings are comparable to those of other photoinvestigation centres, such as the Scottish Photobiology service, where commonly found culprits of drug-induced photosensitivity included thiazide diuretics, amiodarone, NSAIDs, quinine, doxycycline and calcium channel antagonists. Commonly reported culprits of systemic drug-induced photosensitivity in the literature include diuretics, specific antibiotics, antifungals, antipsychotics, calcium channel antagonists, amiodarone, retinoids, quinine and NSAID, which remained culprits in our review. However, our analysis also reveals higher frequencies of drug-induced photosensitivity associated with PPI, angiotensin-converting enzyme inhibitors and statins, which were not among the previously reported common culprits, potentially reflecting an increase in prescription of these drugs. A recent review listed 2 reports of suspected drug-induced photosensitivity reactions to the PPI pantoprazole and esomeprazole. Our findings also suggest occasional reactions to drugs that were not included as culprits in a recent review of drug-induced photosensitivity and a systematic review of drug phototoxicity, including the beta-blockers bisoprolol and atenolol (while tilisolol was reported), lamotrigine, phenobarbital, levooxyroxine, allopurinol, colesevelam, parthenolide, tamoxifen, tamsulosin, vitamin B12, nicorandil and gold injection.

Our report has revealed further emerging culprits with previously limited reports in the literature. Sometimes involving younger patients (age < 35), these culprits included azathioprine and biologics, that is TNF-α inhibitors and denosumab. Severe UVA photosensitivity to azathioprine was seen in 3 patients (also in a 4th patient treated with infliximab and azathioprine), contrasting with the more modest skin photosensitivity to UVA previously reported on azathioprine. Perrett et al demonstrated reduced MED to UVA and SSR in a series of 5 patients taking azathioprine, with no abnormal response to UVB. Of concern, azathioprine is also associated with photocarcinogenesis; this is thought to be exerted through metabolites such as 6-thioguanine causing promutagenic oxidative DNA damage following interaction with UVA.

Our series also revealed one case of etanercept-induced photosensitivity to UVA, and a further case of possible potentiation of UVA and UVB photosensitivity to azathioprine by infliximab. TNF-α inhibitors have been associated with a variety of cutaneous reactions, including psoriasis, sebopsoriasis, pustulosis, eczematous, bullous, granulomatous, lichenoid and vasculitic rashes, and have also been widely associated with drug-induced LE, which may contribute to photosensitivity. However, no similar reports of severe photosensitivity as seen in our cases have, as far as we are aware, been reported.

We found one case of photosensitivity related to denosumab, an anti-RANKL biologic administered subcutaneously to treat osteoporosis. Although there is scarce mention of denosumab-induced photosensitivity in the literature, FDA reports have linked denosumab to photosensitivity; this was seen in 6 treated patients versus 1 on placebo in a phase III randomized clinical trial involving 7800 postmenopausal women with osteoporosis.

In recent years, cases of photosensitivity have been reported with newer drugs including cancer therapies such as BRAF kinase inhibitors, for example vemurafenib and dabrafenib, epidermal growth factor receptor (EGFR) inhibitors and other anticancer therapies. No cases were seen in our photoinvestigation centre in relation to these agents, perhaps due to awareness and management of the cutaneous adverse effects by the oncology community.

What makes certain patients more likely to develop drug-induced photosensitivity is unclear. It is probable that genetic factors, such as polymorphisms in genes encoding drug-metabolizing enzymes, antioxidant properties and sensitivity to UVR play a role. We found the gender balance of patients to be equal (female 52.5%, n = 64). The median age was 62 years, reflecting that older patients are more likely to be on medications, especially multiple medications, thus increasing their risk of drug-induced photosensitivity.

Drug-induced photosensitivity had a very large or extremely large impact on patients’ QoL in half of patients completing the questionnaire, with a median DLQI of 11 for the past year for all patients. This was comparable to other photodermatoses, where median DLQI scores of greater than 10 for the past year were seen, for example, in actinic prurigo and photoaggravated dermatoses in a multicentre assessment of 790 patients with photodermatoses. QoL in drug-induced photodermatosis was also assessed in a cohort of 26 patients in that multicentre study, although this was conducted by postal questionnaire at a time point subsequent to patient diagnosis. It was found that 23% of patients scored a DLQI of >10, compared to 51% of 58 patients who completed the DLQI questionnaire at the time of photoinvestigation in our patients.

In our series, phototesting via monochromated and broadband UVR provides an objective method of confirming photosensitivity, alongside a typical clinical history and evaluation for drug photosensitivity. Nearly half, that is 45.1% patients, had reduced MED on monochromator phototesting. Some patients had already stopped taking the culprit drug before attending the photodiagnostic unit, potentially explaining their normal MED on monochromator phototesting. Interestingly, the yield of abnormal responses was increased by the addition of broadband phototesting; this might be anticipated in view of the broad action spectrum demonstrated by several phototoxic drugs. The majority of lowered MED were to UVA alone, and while a number occurred to UVB in addition to UVA, none were seen to UVB alone (Table 3). Only one patient, taking bendroflumethiazide, showed lowered MED to UVA plus visible light. This action spectrum was anticipated, that is reflecting the frequency of UVA > UVB > visible light activation.

Limitations of this study include the challenges in identifying culprit drugs in patients who take several medications and where a concurrent photodermatoses, such as photoaggravated eczema, may confound presentation. There is no definitive diagnostic test for drug photosensitivity, and consequently, this diagnosis is inevitably largely presumed rather than proven. It would be optimal for photodiagnostic units to follow up all patients suspected of drug photosensitivity, including repeat phototesting, although this is often not practically possible. All our patients are offered follow-up appointments, but as many travel long-distance to the specialist unit, they often arrange to return only if their symptoms persist, deferring their appointment if they resolve.
In conclusion, we find drug-induced photosensitivity occurred in 5.4% patients referred to a specialist photoinvestigation unit and suspect a much larger population of patients fails to be suspected and referred. Classical photosensitizing drugs such as quinine and thiazides remain common culprits; physicians should be aware of these as well as emerging culprits including the biologics, PPI and statins. Drug-induced photosensitivity causes very high impact on QoL and is vital to suspect in view of its potentially curable nature. Early suspicion, identification, consideration of phototesting/repeat phototesting alongside cessation of culprit drugs where feasible, and implementation of photoprotection, are key measures.

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CONFLICT OF INTEREST
None declared.

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