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Dear Friends and Colleagues,



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More than three years have passed since we all met at our World Photodermatology Day in June 2019 at the WCD Milan. We went through a dark period due to the Covid pandemic and our usual meetings for the Annual Photodermatology Day were held as virtual events. This was better than nothing, but we all missed the ambiance of the “in presence” meetings, we could not interact properly and could not discuss face to face and shake hands.

Now light is coming back and this is good also for Photodermatology... To restart, we have decided to publish part of the abstracts that were presented at the World Photodermatology Day 2019 in Milan and one abstract for each one of the Photodermatology Day meetings that followed the WCD in Milan. All this illustrates that in Photodermatology the sun never sets.

Photodermatology is the scientific discipline that deals with how sunlight or parts of it, in particular the ultraviolet (UV) band, affects the skin, our directly visible, frontier organ facing our environment. Although this discipline would appear well within the domain of our everyday experience, many of the basic processes involved are still not fully charted and understood. Concerning therapeutic approaches, the term photomedicine has been coined, also because some of the effects of light go far beyond the skin, and light administration is also used in medicine in general. This special issue aims to present a selection of topics to provide a bird’s eye view of the field.

An area of broad public interest is represented by the photodermatoses: in this chapter, of note, is the lecture on “**Quality of life and psychological impact of the photodermatoses**” by Dr. Kirsty Rutter from the Photobiology Unit, Salford Royal Hospital, University of Manchester, UK, that sheds light on the consequences that these widespread diseases can have on the life of patients and their behavior. In the same area, we present an update on “**diagnostic photo testing**” by Prof. Sally Ibbotson, who gave also an interesting lecture on “**Drug induced photosensitivity and photocarcinogenesis**” at the World Photodermatology Day in Milan.

Another very interesting invited lecture at the WCD Milan 2019 was that of Yolanda Gilaberte and coll. on “**PDT for infectious diseases**” discussing the possible applications of PDT in the treatment of cutaneous infections.

Kolbe and coll. in their lecture at the WCD in Milan “**Skin photo-protection by Nrf2-induction - A line of defense against high energy visible light-induced oxidative stress**” discuss protection of the skin to wavelengths beyond UV, like high energy visible light (HEVIS) by a novel generation of topical agents that boost protective mechanisms of the skin, namely due to the effect of adding antioxidants.

Gelmetti and Calzavara in their lecture at the WCD in Milan, “**Phototherapy in the age of biologics: keeping up with the new therapies**”, provided an excellent perspective on the main indications for use of narrowband UVB (311–313 nm) as related to the use of modern systemic therapies, like biologics, and provided comparative information on one of the most well-known and longstanding dermatological treatments, which, despite the introduction of biologics continues to remain invaluable for many conditions such as psoriasis, atopic eczema, vitiligo, and cutaneous T cell lymphoma.

Another important lecture on “**Vitamin D and melanoma**” was given at the WCD 2019 by Prof. Marjan Garmyn: is there a possible protective effect of VD on melanoma outcome? This is supported by in vitro studies and small animal studies, but it has to be confirmed with large-scale studies in humans.

Nowadays a topic of great interest is represented by the environmental impact of sunscreen use and this has been presented and discussed in “**Environmental Threat due to Sunscreens.**” by Henry W. Lim, from Detroit, Michigan, USA, in his invited lecture at the ESPD Virtual Photodermatology Day in October 2020.

Last but not least, Cheng-Che Eric Lan, from the Department of Dermatology, Kaohsiung Medical, Taiwan, gave a superb overview of the “**Effects of photon density on UVA-induced photoaging**” at the WCD in Milan, where he described how the biological effects of equivalent UVA fluence administered at different irradiance on the skin can influence the effect of UVA-induced skin aging related to sunscreen use.

I am excited to present this issue of Flash on Photodermatology, which intends to be as updated as possible while presenting and discussing some of the topics that are related to the interaction between human skin and light.

Thanks to all our presenters for their contribution and continued passion in this area. I hope that your reading will only stimulate more questions, which our specialty will answer together. Enjoy!

Rome, June 2022



Drug photosensitivity today - culprits, impact and investigation

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Systemic drugs are a potentially reversible cause of photosensitivity.

Aim: Our objectives were to explore prevalence, impact, phototest findings, current and emerging culprits of drug-induced photosensitivity.

Methods: A retrospective study was performed of patients diagnosed with drug-induced photosensitivity (2000-2016) in a specialist photoinvestigation centre, using data recorded in standardised proforma. Patients underwent phototesting with broadband UVR (UVA; SSR) and monochromator testing to narrowband UVR and visible radiation. Laboratory tests excluded connective tissue disease and porphyria. Dermatology Life Quality Index (DLQI) was evaluated.

Results: The prevalence of drug-induced photosensitivity was 5.4% (122/2243) of patients presenting with photosensitivity. These were: 52% female; median age 62 years (range 11-86); phototype I (17.2%), II (39.3%), III (26.2%), IV (6.5%) and V (4.1%). 92% patients had positive responses to broadband UVR; 38% (46/122) showed reduced erythema thresholds to monochromator testing with UVA, 7% (n=9) to UVA and UVB, and 0.8% (n=1) to UVA and visible light. Culprits implicated were: diuretics 12.2% (thiazide 10.6%), quinine (12.3%), antifungals (9.8%; voriconazole, terbinafine),

proton-pump-inhibitors (9.8%), angiotensin-converting-enzyme-inhibitors (8.2%), statins (5.7%), selective-serotonin-uptake-inhibitors (4.9%), anti-inflammatory-drugs (4%), antiepileptics (3.3%), antibiotics (2.5%), beta-blockers (3.3%), tricyclic-antidepressants (3.3%), calcium-channel-antagonists (4.9%); several other drugs (<1.6% cases each). Emerging culprits included azathioprine (2.5%) and monoclonal antibodies- etanercept, denosumab and infliximab (2.5%). Mean DLQI was 13 (range 2-27).

Conclusion: In conclusion, our study reveals emerging culprits of drug-induced photosensitivity. Usefulness of broadband in addition to monochromator phototesting is highlighted. There is very large impact on life quality; identification enables measures including drug cessation and implementation of photoprotection.



Clinical and non-invasive evaluation of a case of Graham-Little-Piccardi-Lassueur Syndrome treated with nb-UVB phototherapy

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Graham-Little-Piccardi-Lassueur Syndrome (GLPLS) is a type of lichen planopilaris characterized by the triad of follicular spinous papules on the body area, scarring alopecia of the scalp and non-scarring alopecia of the groin and/or axilla.

Aim: Clinical and non-invasive evaluation of response of a case of Graham-Little-Piccardi-Lassueur Syndrome treated with nb-UVB.

Methods: A 45 year-old female presented to our Dermatology department with cutaneous rash on her neck, trunk and limbs since 13 years.

Past medical history was non-contributory. Family history was positive for psoriasis in the sister. Treatment history included topical steroids and oral antihistamines, without relief.

A 5mm punch skin biopsy was performed. Diagnosis of lichen spinulosus was made.

On examination, alopecia of the scalp, pubis region and axillae was noted.

A biopsy of the scalp was diagnostic for 'scarring alopecia', while clinical examination of pubis and axillae was suggestive for a non-scarring type.

Results: Histological findings were compared with dermoscopic and reflectance confocal microscopy images.

Based on the above findings, diagnosis of Graham-Little-Piccardi-Lassueur Syndrome was made, and the patient was started on treatment with nb-UVB phototherapy twice a week, in association with topical steroids and emollients. Non-invasive evaluation was repeated after treatment, revealing reduction of inflammation and hyperkeratosis. Furthermore, significant improvement of quality of life was reported by the patient.

Conclusion: This is the first case of Graham-Little-Piccardi-Lassueur Syndrome in which confocal microscopy and dermoscopic features were assessed before and after nb-UVB phototherapy.



PDT for infectious diseases

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Photodynamic therapy (PDT) is a different approach to treat infections because instead of being directed against a specific target in the microorganism, as conventional antimicrobials, it is a multitarget therapy. Although antimicrobial PDT (aPDT) is effective against bacteria, viruses, fungi and parasites, Gram-positive bacteria are easier to kill than Gram-negative bacteria and fungi. PDT is also effective against resistant bacterias and biofilms.

Aim: To present the applications of PDT in dermatological infectious.

Methods: The photosensitizers more commonly used for aPDT are aminolevulinic acid (ALA) and its methyl derivative (MAL), methylene blue (MB) and phthalocyanines. Regarding light sources, blue or red LEDs lamps, daylight or even laser fibre optics have been used.

Results: PDT has been used to be effective for chronic ulcers; several clinical studies conclude that PDT accelerate wound healing, reduces significantly the germ load, without significant side effects or systemic absorption. Onychomycosis is another infection susceptible to be treated with PDT, either those caused by dermatophytes or nondermatophyte molds; pre-treatment either with urea 40% for several days or total avulsion of the nail plate is needed in order to facilitate the penetration of the photosensitizer. PDT is also very useful in the management of hair follicle infectious diseases such as acne and hidradenitis suppurativa. In acne, ALA or MAL induce the accumulation of PpIX in the sebaceous gland and eradicate

Pacnes. In hidradenitis suppurativa, intralesional PDT using ALA 1% gel and intralesional laser 630 nm achieved a complete response in 37% patients and only 4% did not improve. PDT can be used for refractory hand/foot warts (level of evidence IB) and refractory genital warts (level of evidence IB). Finally, cutaneous leishmaniasis is one of the most promising antimicrobial applications of PDT (level of evidence IB).

Limitations: aPDT is only useful for localized superficial infections; it is more time consuming for doctors than the prescription of conventional antimicrobials, and some microorganism can survive after PDT and regrow again. For that reason, the combination of PDT with conventional microorganism can be a way to overcome this latter limitation.

Conclusion: aPDT is especially useful for infected chronic wounds, follicular and nail infections and also cutaneous leishmaniasis. Clinical trials are needed in order to determine specific photosensitizers and protocols for different infections.



Skin photo-protection by Nrf2-induction - A line of defense against high energy visible light induced oxidative stress

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R&D Beiersdorf AG

Currently, skin photo-protection primarily focuses on the UV-portion of the solar spectrum since the high energy of UV-radiation induces skin damage after a short time of exposure. However, also high energy visible light (HEVIS, 400-500 nm) significantly affects skin physiology. Since conventional UV filters do not protect against visible light, other means of photo-protection are needed to counteract HEVIS-induced reactive oxygen species (ROS) production.

Aim: The aim of the study was to investigate the efficacy of antioxidants against HEVIS-induced ROS.

Methods: Cultured human skin cells were irradiated with VIS(>400nm), in doses and intensities comparable to one hour of sunlight to induce oxidative stress after pre-incubation with various anti-oxidants. Cellular ROS status was measured using a DCF assay. The KeratinoSens™ cell line was used to determine the Nrf2-inducing potential of anti-oxidants. Prior to testing, cells were incubated for 24 hours with the test substances.

Results: Irradiation with VIS induced considerable oxidative stress. In contrast, infrared radiation, even at very high doses and intensities, did not induce any oxidative stress in cell cultures. Pretreatment of skin fibroblasts with the Nrf2-inducer Licochalcone A significantly reduced VIS-induced ROS at low concentrations. Surprisingly, classical radical

scavenger like Vitamin C and its derivatives ascorbyl-palmitate and ascorbyl-phosphate, which do not induce Nrf2, did not significantly reduce VIS-induced ROS.

Conclusion: Antioxidants are important additive ingredients in sun-protection products. However, not all antioxidants are effective against HEVIS-induced ROS at relevant concentrations and Nrf2-induction seems to be an important mechanism to stimulate endogenous skin photo-protection.



Clinico-functional and morphologic evaluation of eosinophilic fasciitis and response to UVA-1 phototherapy: high frequency skin ultrasound, skin microbiopsy and molecular investigations

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Eosinophilic fasciitis is a rare autoimmune-disease causing progressive induration of dermal, hypodermal and muscularis fascia of the trunk and extremities.

The onset includes aspecific symptoms such as low-grade fever, swelling erythema or firm oedema of the extremities, muscular and articular pains, asthenia. Most of cases are correctly diagnosed once the disease has progressed to a chronic phase, characterized by a fibrous-cicatricial substitution of the subcutaneous tissue with retraction of the overlying skin, causing the typical «orange peel» sign and joint contractures (especially to the elbows, wrists, knees, shoulders) plus arthralgia. Frequent complications include: tendon contractures and retraction (i.e., the “prayer sign”), carpal tunnel syndrome (about 25% of pts), dispigmentary or sclerotic outcomes (especially on the trunk).¹⁻³ The exact pathogenesis is yet to be fully understood: it is supposed that a certain trigger (often a trauma, less frequently a drug or a

parasite infection) stimulates an autoinflammatory local fibrotic reaction of the external muscularis fascia further involving the overlying subcutaneous tissue. A specific therapy still lacks, and patients are treated with standard immunosuppressive protocol based on prednisone in combination with methotrexate usually for a long time. Encouraging results were obtained in the last years with whole-body irradiation with high-dose UVA-1 phototherapy for the treatment of the subcutaneous inflammatory disease.⁴⁻⁷ However, due to the rarity and/or the rates of underdiagnosis, these patients are still poorly characterize to date, either before end in course of therapy.

Aim: To obtain a clinico-functional characterization of EF patients treated with adjuvant high-dose UVA-1 irradiation.

Methods: A total of 11 patients (7 males, 4 females, average age 45 years), candidates to standard therapy (prednisone + mtx) were enrolled. We treated with standard UVA-1 protocol (70j/cm², 4 times/week for 40 sessions). The timeline for examinations included 8 consecutive moments (t): baseline (t0), last irradiation session (t1), 2-weeks after t1 (t2), 1 month after t1 (t3), 2 months after t1 (t4), 3 months after t1 (t5), 6 months after t1 (t6), 9 months after t1 (t7). Clinical picture for body lesion mapping, Localized Scleroderma Assessment Tool (LoSCAT) and Dermatology Life quality Index (DLQI) scores were calculated at each examination time t0-t7. High Frequency Ultrasound (HFUS) (MyLab™ 50 Esaote biomedica®, linear probes 22MHz and 13-17MHz) and ultra HFUS (VEVO MD®, Visualsonics Fujifilm, linear probe 55-70 MHz) were employed to monitor dermal, hypodermal and fascial thickness at t0, t5 and t7. Five repere points were estimated, along with corresponding contralateral healthy point 8 were possible). Both classical incisional biopsy and micro-invasive bioptic technique were performed for histological and molecular analysis, at t0 and t5. Primary cell cultures were obtained from these lesional bioptic explants and further amplified for rtPCR and western Blot analyses: the RNA expression of a panel of pro-fibrotic and pro-inflammatory cytokines (i.e., IL-1 β , CTGF, TGF β 1, smad2-3, Grb2, TGF β receptor II, TNRSF12A) and of collagen types (I, III, VIII, X, XII) were investigated, along with a panel of anti-fibrotic molecules involved in tissue remodelling (i.e., CTHRC1, TIMP-1 and MMP-1,2,7,8,9,12). In vitro UVA-1 irradiation of primary lesional cell cultures obtained at t0 and t5 was also realized (Thermo-orient® Solar Simulator, 150W Xenon Lamp) on confluent cells monolayer (~650.000 cells/petri dish 3.5cm). Control group for laboratory investigations was composed by healthy tissue harvested from the same body sites in patients undergoing surgery, matched for age and sex.

Results: LoSCAT and DLQI scores were adequately correlated with quantitative (i.e., thickness) and qualitative (i.e., inflammatory aspects) assessments of HFUS imaging. A significant reduction in thickness of lesional tissue, less residual pigmentation and an increase in elasticity and joint mobility. The average LoSCAT score was 150 at t0, decreased to 30 at t7. Compared with t0, the echographic reduction of lesional dermis and external muscularis fascia at t7 were -45% and -60%, respectively. At the thigh repere point (T),

the average thickness value for dermis and muscularis fascia were 1.2 \pm 0.7mm and 1.4 \pm 0.2 at t0, while 0.8 \pm 0.2 and 0.5 \pm 0.1 at t7. Laboratory evaluations of baseline and irradiated lesional primary cultures showed that: lesional fibroblasts proliferation was enhanced compared with healthy coltures; UVA-1 does not affect cells viability and proliferation in vitro. Molecular investigations on primary cells irradiated in vivo, compared with baseline, showed an up-regulation in the expression of CTHRC1 and all MMPs, especially MMP-1,2 and 9, meaning an enhanced fibrolysis and matrix digestion, due to a significant reduction in TIMP-1. Of converse, TGF β receptor II, smad2-3, Grb2 and TNRSF12A were downregulated. Of note, the stimulatory pathway IL-1 β \rightarrow TGF β 1 \rightarrow CTGF was significantly inhibited due to a reduction on the expression of IL-1 β (by 6 times), compared with baseline and healthy controls.

Conclusion: Medium-dose UVA-1 demonstrated to be a safe adjuvant therapy for EF patients with multiple both in vivo and in vitro. A significant improvement in skin compressibility and dermal elasticity was observed starting from 2-3 months after last irradiation and was maintained in the following 9 months. At tissue level, UVA-1 rays seem to enhance in lesional fibroblasts both an up-regulation of key molecules for matrix digestion and remodelling, and to inhibit the expression of relevant of pro-fibrotic and pro-inflammatory pathways.

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Environmental Threat due to Sunscreens



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Bleaching of coral reefs is a worldwide concern. Based on data generated in laboratory settings, oxybenzone, a widely used UVB and short UVA filter, has been demonstrated to kill adult coral reefs, and deforms DNA in their larval stage¹. It has been proposed that UV filters activates coral viruses, resulting in oxidative stress. This leads to expulsion of symbiotic algae, eventuating in coral bleaching². The lethal concentration-50 for coral cells in vitro has been reported to be in 8-340 parts per billion³.

There are two major routes for UV filters to enter the water in our ecosystem. One is from wash off from skin and clothing during recreational activities, the other is from industrial discharge and waste water effluents⁴.

In a carefully done study by Mitchelmore et al, published in 2019, on concentrations of UV filters in water and coral in Hawaii, it was found that the mean surface seawater concentrations of various UV filters, including oxybenzone, was in parts per trillion range⁵. It should be noted while the concentrations in coral tissues were higher than those in surface water, those were also the same parts per trillion range. These results indicate that that in vitro lethal concentration range was 1,000-fold higher that what was detected in water.

Another study published in 2020 summarized the global occurrence of UV filters in seawater⁴. While the methods varied considerably, in some parts of the world, including the US, Japan and China, the concentrations of some of the filters, most notably benzophenone-3 (oxybenzone), were in the parts per billion range. Clearly, more carefully done studies with consistent methodologies need to be performed.

Other concerns for the presence of organic filters in seawater are bioaccumulation and biomagnification¹. Bioaccumulation refers to chemicals reaching higher concentrations in organisms than those in the environment. Biomagnification refers to chemicals becoming more concentrated as one moves higher up in the food chain. Low levels of oxybenzone and octinoxate had been reported to be detected in various species of fish worldwide.

There are many studies concluding that ocean warming and acidification of ocean water are the major causes of coral reefs bleaching⁶. However, because of the controversies, sales of sunscreens containing oxybenzone and octinoxate are banned in the State of Hawaii starting in Jan, 2021. Sunscreens containing some organic filters are also banned in US Virgin Island, Palau. As of Oct 2022, all sunscreens containing organic filters are banned in Maui county.

Absorption of UV filters is another topic that has generated a lot of discussion. Two studies done by FDA scientists showed the presence of all six organic filters in the plasma even after a single application. The studies were performed utilizing a Maximal

Usage Trial (MUST) design, in which 2 mg/cm² of sunscreen was applied to 75% of body surface^{7,8}. The authors clearly stated in both articles that the clinical significance of these findings need further studies, and these results “do not indicate that individuals should refrain from the use of sunscreens.”

Due partly to the data on systemic absorption, the FDA has placed 12 of the currently approved filters in a Not GRASE (generally recognized as safe and effective) status, requesting additional safety data for these filters.⁹

With these controversies and public concerns, it is important for us dermatologists to continue to convey proper photoprotection message:

1. Adverse effects of acute and chronic sun exposure are well known;
2. There are many benefits of outdoor activities. However, practice of photoprotection is essential:
 - a. Seek shade when outdoor;
 - b. Wear photoprotective clothing, wide-brimmed hat and sunglasses;
 - c. Apply SPF \geq 30, broad spectrum, tinted sunscreens (to protect against visible light) to otherwise exposed area.

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Effects of photon density on UVA-induced photoaging

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Ultraviolet A (UVA) radiation is the major external factor that causes skin aging. Sunscreens were developed to reduce UV photon from penetrating the skin (similar to reduction of irradiance (W/cm²)), therefore providing protection.

Previously, we had shown that erythema response from the UVB radiation depend on fluence (J/cm²) but not irradiance. Therefore, development of sunburn indicates certain threshold UV fluence was received by the skin. In other words, development of sunburn indicates equivalent fluence of UV radiation has been received by the skin, with or without sunscreen use (independent of irradiance), even though sunscreen use prolongs the duration required. Unlike sunburn, we had also shown that equivalent UVB fluence delivered at different irradiance has different impact on UVB-induced photocarcinogenesis of the skin.

Our results provide a rationale explaining why increased sunscreen use was not associated with reduction of skin cancers in the real world settings. Examining the biological effects of equivalent UVA fluence administered at different irradiance on the skin would give further insights regarding how

UVA-induce skin aging relates to sunscreen use. At equivalent fluence, low irradiance UVA (LIUVA) significantly reduced collagen production and increased matrix metalloproteinase-1 - expressions in cultured dermal fibroblasts as compared to their high irradiance UVA (HIUVA) treated counterparts.

These in vitro findings were subsequently validated on the animal skin. Increased oxidative stress induced by LIUVA as compared to HIUVA at equivalent fluence appeared to play an important role in this process. In summary, although sunscreen use is the most common way for the public to reduce sun-induced skin damage, more damage to the skin may be produced if sunscreen use is associated with prolonged duration of sun exposure. General public should be made aware of this scenario.



Photodamage of skin and brain

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Our skin is the largest organ of the body and a front-line barrier to the external environment. There is a strong association between the skin and the brain. Once stress such as UV hits the skin, skin senses the stresses, then skin produce various hormones and mediators into the blood circulation, which will reach to the brain through blood-brain barrier penetration. Then, brain functions will be affected by skin-derived hormones and mediators. For example, it has been known that skin-derived vitamin D or β -endorphin after UV irradiation make alter our brain functions.

Recent studies have shown that UV irradiation leads to increases in the blood levels of glucocorticoid by activating central and cutaneous HPA axis. Increased circulating cortisol is a common marker of stress and it has been known that increased cortisol would lead to the suppression of adult neurogenesis. However, it is still unknown whether UV irradiation to the skin affects the function of brain, especially hippocampus functions. Therefore, we decided to investigate whether UV exposure to the skin could affect neurogenesis in the hippocampus and its functions. Hippocampus is involved in memory function and emotion-related behaviors.

Female C57BL/6 mice were irradiated to UV light 3 times a week for 2 weeks. 200 mJ/cm² of UV light was applied to the dorsal skin under anesthesia. We demonstrated that 2 weeks of UV irradiation to the skin significantly decreased the numbers of doublecortin-positive immature neurons in the hippocampal dentate gyrus, when compared to the sham-irradiated mice. This result indicates that repeated UV exposure to the skin can lead

to decreased hippocampal neurogenesis. We also demonstrated that 2 weeks of UV irradiation to the mice skin significantly decreased the expression levels of synaptic proteins, including NMDAR and PSD-95, in the hippocampus. Next, we demonstrated that UV irradiation of the skin increases circulating corticosterone in the serum, via central and cutaneous HPA axes activation, which then bound to glucocorticoid receptors in the hippocampus, leading to decrease of hippocampal neurogenesis and the levels of synaptic proteins.

In conclusion, our data suggest that chronic UV stimulation through the skin causes a decrease in neurogenesis and synaptic density in the hippocampus, resulting in indirect photodamage to the brain. Therefore, we should avoid sunlight exposure to prevent UV-induced hippocampal damages.



Vitamin D and melanoma

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Vitamin D (from the food, via supplements or produced by UVB in the skin) is biologically inert and the biological effect of vitamin D (VD) results only as a consequence of its sequential metabolisation in the liver into 25-hydroxy-vitamin D3 (25(OH)D3) and then in the kidney into the steroid hormone, 1alpha,25-dihydroxyvitamin D3 (1,25(OH)2D3). The classical signaling pathway of 1,25(OH)2D employs the vitamin D receptor (VDR), which is a transcription factor for 1,25(OH)2D3 target genes.

The classical function of VD is its role in bone metabolism. However, VD has also other functions such as effect on immunity (promotes innate immunity and inhibits adaptive immunity) and growth regulation (VD has antiproliferative and pro differentiating effects and induces controlled cell death or apoptosis). This growth regulating effect is responsible for the presumed anticancer effect of VD also for melanoma.

Studies looking at the association of vitamin D levels with melanoma risk are challenging since the measurement of 25-OH-D level is confounded by sunlight exposure, which is a major risk factor for the development of melanoma. This is illustrated by prospective cohort study (Afzal et al., 2013) and nested case control study (Kwon et al, 2018), demonstrating that increased VD levels were associated with increased melanoma risk.

A possible protective effect of VD on melanoma outcome is supported by in vitro studies and small animal studies. Supplementation studies on melanoma cell cultures show antiproliferative effects, inhibition of epithelial mesenchymal transition (EMT), induction of apoptosis and induction of differentiation. Supplementation studies on small animals, have demonstrated an anti-tumor effect on mouse xenografts (Egan et al, 2009). A very recent systematic review and meta-analysis confirms that VD deficiency is associated with higher Breslow and melanoma specific mortality (Tsai et al, 2020). Finally interventional phase Ib-II studies have been started to look at safety, feasibility and possible protective effect of VD supplementation on outcome (Saw et al, 2014; De Smedt et al, 2017)

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Phototherapy in the age of biologics: keeping up with the new therapies



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The prevalence of narrow-band ultraviolet B (NB-UVB) use in Europe to treat moderate and severe psoriasis is unknown, because national registries for psoriasis do not monitor this treatment. In order to investigate the role of phototherapy nowadays (the so called age of biologic drugs), we conducted a prospective 5-years cohort study enrolling 1090 patients suffering from moderate to severe psoriasis (the average Psoriasis Area Severity Index (PASI) score at the first examination was 15.8) without arthritis. The aim of the study was to describe treatment allocation considering NB-UVB among first-line treatment options and rigorously applying EMA criteria for eligibility to biologics that were valid until 2017, in a tertiary referral center that is the only one in the area that is equipped with phototherapy facilities and the only one that is authorized to prescribe biologics.

Table 1 reports all the therapies delivered to the enrolled patients at subsequent treatment cycles.

Concerning phototherapy, it resulted clear how NB-UVB phototherapy has maintained a very important role in the treatment of moderate and severe psoriasis despite the availability of an increasing array of biological drugs. Indeed, the present cohort of 1090 patients received 1047 (54.1%) phototherapy cycles among a total of 1936 treatment cycles, nine hundred and sixteen of which (87.5%) were successful. Phototherapy was delivered at least once to 754 (69.2%) patients, and 595 of them (54.6%) were treated

exclusively with 1 or more cycles of phototherapy and never required a systemic conventional or biologic drug. Only 12.6% of the whole cohort was deemed eligible for a biologic while 32.8% received at least 1 therapeutic cycle with a conventional systemic therapy but never a biologic drug.

Unfortunately, we cannot compare our present results with findings of neither national nor european registries for psoriasis. In fact, the first ones enroll only patients who are treated with systemic treatments and exclude phototherapy while, in the other ones, rates varies widely because of the

	1 st cycle	2 nd cycle	3 rd cycle	4 th cycle	5 th cycle	6 th cycle
Number of patients	1 090 (100%)	445 (100%)	231 (100%)	117 (100%)	43 (100%)	10 (100%)
NB-UVB phototherapy ¹	714 (65,5%)	202 (45,4%)	84 (36,4%)	35 (29,9%)	8 (18,6%)	4 (40%)
DMARDs	300 (27,5%)	185 (41,6%)	92 (39,8%)	50 (42,7%)	20 (46,5%)	3 (30%)
PUVA	133 (12,2%)	68 (15,3%)	29 (12,6%)	25 (21,4%)	11 (25,6%)	
Acitretin	48 (4,4%)	41 (9,2%)	16 (6,9%)	7 (6%)	1 (2,3%)	1 (10%)
Cyclosporine	53 (4,9%)	38 (8,5%)	16 (6,9%)	6 (5,1%)	4 (9,3%)	
Methotrexate	66 (6,1%)	38 (8,5%)	31 (13,4%)	12 (10,2%)	4 (9,3%)	2 (20%)
Biologics	76 (7%) ²	58 (13%) ²	55 (23,8%) ²	32 (27,4%) ²	15 (34,9%) ²	3 (30%) ²
Adalimumab	20 (1,8%)	23 (5,2%)	22 (9,5%)	18 (15,4%)	7 (16,3%)	1 (10%)
Etanercept	40 (3,7%)	25 (5,6%)	10 (4,3%)	6 (5,1%)	1 (2,3%)	
Ustekinumab	9 (0,8%)	4 (0,9%)	11 (4,8%)	3 (2,6)	3 (7%)	
Infliximab	2 (0,2%)	1 (0,2%)				
Golimumab	1 (0,1%)	1 (0,2%)				
Secukinumab	4 (0,4%)	4 (0,9%)	12 (5,2%)	5 (4,3%)	4 (9,3%)	2 (20%)

DMARDs, disease-modifying antirheumatic drugs; PUVA, psoralen plus ultraviolet A. 1. 595 patients treated only with NB-UVB phototherapy are part of 754 patients who underwent at least 1 NB-UVB phototherapy cycle. 2. Patients who received at least 1 treatment cycle with a biologic were 137: 76, 22, 21, 12, 6 at the 1st, 2nd, 3rd, 4th and 5th treatment cycles, respectively

TABLE 1

Therapeutic options that were delivered to patients at subsequent treatment cycles 1–6

influence of several parameters such as different durations of observation and differences in the access to phototherapy. In addition to that, unlike ours, the results of some cited registers referred to years before 2010 while the use of biologics has grown in the following years in all European countries.

In conclusion, in our experience supported by the present study, phototherapy remains a mainstay of the management of moderate to severe psoriasis, and about half of our patients were treated with it. In the absence of randomized and controlled com-

parative studies, we cannot know, if and how much NB-UVB is less effective than systemic treatment options, including biologics. However, it can be stated that not only it is much cheaper than biologics, but most of all its safety profile is very good and allows to treat some patients who could not be treated with any other treatment except for topicals.



Diagnostic Phototesting

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It may be obvious to the patient that sunlight is the cause of their skin problems, for example in polymorphic light eruption, but in many cases this is not clear-cut. Indeed on clinical presentation and assessment alone it may not be apparent that the diagnosis is a photosensitivity disease and patients, primary care physicians and even dermatologists may be puzzled.

From our patient engagement work we have elicited that this can lead to lengthy delays in diagnosis and patients may be left frustrated and feeling that they are not being taken seriously. In order to establish an accurate diagnosis of photosensitivity, or indeed to rule this out, and to optimise management it is therefore essential that photodiagnostic investigations are available for patients with suspected photosensitivity diseases. Photodiagnostic services are not available in all dermatology departments as they are limited to tertiary services due to the requirement for specific equipment and expertise. However, all dermatologists should have access to a photodiagnostic unit to enable referral, investigation and management of patients with suspected photosensitivity.

In the UK, Photodiagnostic services developed in the early 1970's and there are currently 12 photodiagnostic units (one in development) in the UK and Republic of Ireland. However, there is limited literature and no formal guidance on photodiagnostic methodology in terms of the nature and delivery of these services. We therefore held a British Photodermatology Group/ British Association of Dermatologists Workshop to review the situation with respect to the provision of photodiagnostic techniques in the UK, in order to assess current practices and to initiate the development of consensus practices (Ibbotson et al., J Eur Acad Derm Venereol 2021;35: 2448-2455). The findings

of this Workshop review reinforced the importance of the availability of expertise and dedicated staff for photodiagnostics, both clinically and in photophysics, and through the roles of clinical scientists and allied healthcare professionals. Dedicated equipment is essential in order to enable accurate and detailed investigation of patients with suspected photosensitivity disorders. Narrow waveband testing in the form of monochromator phototesting is currently the Gold Standard investigation with respect to establishing the action spectrum and degree of photosensitivity and assessing treatment response and natural history of photosensitivity. However, this is often also supplemented by broader band phototesting to establish objective photosensitivity. Most photodiagnostic units also offer iterative provocation (Figure 1) and



FIGURE 1:
Broadband UVA iterative provocation testing – showing positive provocation of polymorphic light eruption

minimal erythema dose (MED) testing investigations, along with patch testing and photopatch testing to define coexistent allergens and photoallergens and other investigations to exclude less common causes of photosensitivity, such as lupus, cutaneous porphyrias and the genophotodermatoses.

The Workshop review enabled us to identify key areas of consensus practice, which we consider to be an important step towards the process of standardising and optimising procedures and protocols and to esta-

blish minimum clinical standards for photodiagnostic services. The review additionally provided us with key areas to focus on in terms of clinical service development, research and training and we consider that the same principles will be broadly applicable to photodiagnostic services throughout Europe and beyond.



Drug induced photosensitivity and photocarcinogenesis

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Most drugs used in clinical medicine can absorb light and therefore could theoretically cause photosensitivity.

In general, abnormal photosensitivity induced by photoactive drugs is considered as an adverse effect, although it can be used in a controlled and repeated way for therapeutic purposes, such as with psoralen-UVA photochemotherapy or photodynamic therapy. Most drugs which are administered systemically will cause photosensitivity reactions through a non-immunological and phototoxic mechanism. This can theoretically occur in anyone exposed to enough drug and light of the appropriate wavelengths. Phototoxic reactions can occur on first exposure and dose-dependency is usually apparent, and this should be reversible on stopping the drug.

Photoallergic reactions to drugs are less well understood and photoallergy to systemic drugs is poorly defined. Most drug photoallergy occurs in the context of topical photocontact allergic dermatitis occurring to topically applied photoallergens. The underlying mechanism is considered to be a Type IV-delayed hypersensitivity reaction. Sensitisation is required and subsequent minute exposure to photoallergen can trigger the reaction. In current usage, the main culprits for topical photoallergy are absorbent sunscreen chemicals and non-steroidal anti-inflammatory drugs, such as ketoprofen or etofenamate.

There are also less common mechanisms for drug-induced photosensitivity, such as through a lupus or lichenoid pathway and pseudoporphyria, which can be a mimic of porphyria cutanea tarda, although porphyrins will be normal and pseudoporphyria appears to be caused by phototoxic insult at the basement membrane.

There are a variety of ways in which drug phototoxicity can present ranging from a tingling, prickling sensation or an exaggerated sunburn, such as with chlorpromazine, doxycycline or thiazide diuretics, through to a delayed erythema as seen with psoralens or photoexposed site telangiectasia due to photoactive metabolite with calcium antagonists. Furthermore, whilst stopping the culprit drug should result in resolution of photosensitivity, the interval until resolution will vary widely depending on the drug and whether it is phototoxic reaction to parent drug or metabolite, how quickly the drug is eliminated and its tissue binding. For example, fluoroquinolone phototoxicity will reverse over 24-48 hours on stopping drug, whereas thiazides photosensitivity may take 3-6 months and quinine and amiodarone 9-12 months.

Many cases of drug-induced photosensitivity are not investigated and it is likely that it is more common than estimated from referrals to a specialist photodiagnostic centre, where approximately 5-15% of diagnoses are of drug photosensitivity. Many affected will just stop the drug and substitute for an alternative or may think that they have an abnormal sunburn or reaction to sunscreen. However, for those patients referred for investigation this would be undertaken in centres with photobiology expertise, and the Gold Standard investigation for systemic drug phototoxicity is monochromator phototesting. This is important in distinguishing drug-induced photosensitivity from other causes of photosensitivity, such as chronic actinic dermatitis. Drugs usually photosensitise mainly in the UVA part of the spectrum, sometimes extending into UVB as with thiazides or quinine, or into the visible part of the spectrum as with porphyrins and fluoroquinolones, for example. However, disproportionate UVA photosensitivity on monochromator phototesting does raise suspicions of drug photosensitivity as the underlying diagnosis. Solar simulator phototesting may also be helpful but if only whole spectrum

solar simulator is used then UVA sensitivity can be missed, as the solar simulator is predominantly a UVB-weighted spectrum.

Monochromator phototesting is a key investigation in photosafety studies of drugs under development as this enables clinical phototoxic risk to be investigated if pre-clinical signals in cells and animal models are positive. Photosafety investigations would be undertaken in healthy volunteers using a randomised placebo and positive control robustly designed clinical trial and can be of great importance in terms of establishing whether photosensitivity is a significant risk for a drug in clinical use. Some of the common culprits for drug-induced phototoxicity are fluoroquinolones, doxycycline, demeclocycline, thiazides, quinine, non-steroidal anti-inflammatories and amiodarone as examples. It is also important to emphasise that lupus serology and porphyrin analysis should be performed. The investigation of choice for suspected topical photoallergy is photopatch testing and this can be most informative in defining the culprits for photocontact allergic dermatitis.

Defining phototoxic risk of a drug is important, as for some drugs there is a definite relationship between phototoxicity and photocarcinogenesis, such as with the psoralens, azathioprine and voriconazole. However, for some photoactive drugs, associations with human skin cancer risk are less clearly defined, such as with the thiazides and photoactive tetracyclines.

Thus, in summary, drug-induced photosensitivity is a relatively common adverse effect of many photoactive drugs and can present in diverse ways depending on the mechanisms involved. Investigation and establishing a definitive diagnosis is important as phototoxicity should be reversible on stopping drug. Controlled use of drug phototoxicity therapeutically can be invaluable. Established investigations are available for both suspected systemic drug phototoxicity and topical photocontact allergy through specialised centres of expertise. Further work is required to define possible links between drug phototoxicity and photocarcinogenesis and other potential systemic or ocular risks.



Quality of life and psychological impact of the photodermatoses

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The photodermatoses affect large numbers of people worldwide. They present unique challenges, not only because of the specific clinical features of the conditions, but also because of the marked behavioural modifications that are often required to manage the condition. These include sometimes extreme sun avoidance measures as well as using a variety of sun protection methods (e.g. clothing, hats, sunscreen) impacting on many aspects of daily life.

Our recent systematic review aimed to identify tools that have been used to assess quality of life (QoL) and psychological morbidity in photodermatoses, and to use this information to describe the impact for patients. A systematic search of databases yielded 20 studies which were included in the review; 19 assessing quality of life and 3 assessing psychological function.

The most commonly used tool, the Dermatology Life Quality Index (DLQI) or variants thereof was used in 15 of the included studies. Using this tool, a high proportion of patients with photodermatoses showed a “very large” or “extremely large” impact on their QoL, with 31-39% adult patients having DLQI>10. Particularly high scoring areas for patients with photodermatoses included the impact on social or leisure activities, the ability to do sport, and clothing worn. Certain conditions across a number of studies showed the highest rates of impact on QoL. These included erythropoietic protoporphyria, actinic prurigo, xeroderma pigmentosum and solar urticaria.

A similar, substantial impact on QoL for children with photodermatoses was also found, though fewer studies have been conducted in children.

Single assessments of QoL can be problematic in fluctuating disease. One approach is to use a modified DLQI which adjust questions to reflect impact “over the past year” rather than “over the past week”. Although susceptible to recall bias and unvalidated, modified past year scores were generally higher than past week scores, and this modified tool may better reflect the impact of an intermittent or seasonally aggravated condition. Other possibilities include conducting repeated QoL assessments at different times of the year to capture the impact of seasonal variation.

The impact of photosensitivity on QoL was also highlighted by two studies of cutaneous lupus erythematosus using the Skindex tool: worse QoL was found in patients who were photosensitive versus those who were not, even if they had less clinically

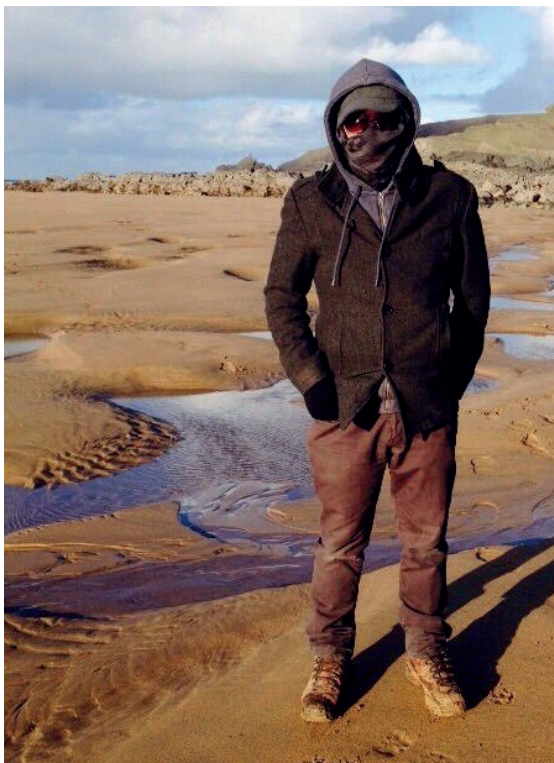
severe disease. Only one tool has been specifically designed for use in photodermatoses – the EPP-QoL. This tool was found to be more sensitive than the DLQI in capturing response to afamelatonide therapy in erythropoietic protoporphyria.

There was a scarcity of studies evaluating psychological morbidity in the photodermatoses. However, available evidence showed that rates of anxiety and depression were around double those in the UK healthy population, with probable anxiety in 22% and probable depression in 8%. Greater predisposition to

psychological morbidity was seen in female patients as well as in those with facial involvement or younger age of onset.

In summary, there is evidence for substantial impact on QoL and psychological health in patients with photodermatoses, which warrants careful consideration and further attention.

Quality of life and psychological impact in the photodermatoses: a systematic review. Rutter KJ, Ashraf I, Cordingley L, Rhodes LE. *Br J Dermatol.* 2020 May;182(5):1092-1102

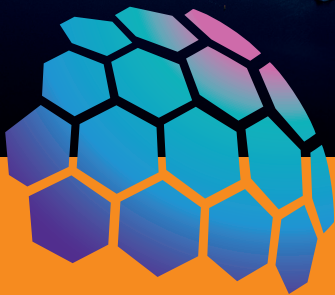


(a)



(b)

This illustrates the severe modifications that adults (a) and children (b) with photosensitivity disorders may need to make, with high negative consequences for their daily lives.



25th World Congress of Dermatology

SINGAPORE 2023

Dear members of the ESPD and colleagues,

We are happy to announce our next “World Photodermatology Day” that will take place at the next WCD 2023 in Singapore, on the first day of the World Congress on July the 3rd 2023, the day dedicated to the Sister Societies meetings.

The World Photodermatology Day 2023 will last the whole day, morning and afternoon, and will include lectures and presentations from experts in the field from all over the world. This time we, as ESPD, are organizing the event together with the US Photodermatology Society.

Be sure to be with us, if you attend the WCD in Singapore, for a fantastic whole day entirely dedicated to the present and the future of Photodermatology. Hopefully as exciting as the previous one in Milan.

See you in Singapore in July 2023 !

**The Board of the ESPD and
the Board of the US Photodermatology Society**



From left to right: Dr. Goh Boon Kee,
Prof. Giovanni Leone,
Prof. Tan Saut Hood &
Prof. Roy Chan (WCD president)

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