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Observational pilot study of multi-wavelength wearable light dosimetry for erythropoietic protoporphyria

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Abstract

Background Erythropoietic protoporphyria (EPP) causes painful light sensitivity, limiting quality of life. Our objective was to develop and validate a wearable light exposure device and correlate measurements with light sensitivity in EPP to predict and prevent symptoms.

Methods A wearable light dosimeter was developed to capture light doses of UVA, blue, and red wavelengths. A prospective observational pilot study was performed in which five EPP patients wore two light dosimeters for 3 weeks, one as a watch, and one as a shirt clip.

Results Standard deviation (SD) increases from the mean in the daily blue light dose increased the odds ratio (OR) for symptom risk more than the self-reported outdoor time (OR 2.76 vs. 2.38) or other wavelengths, and a one SD increase from the mean in the daily blue light wristband device dose increased the OR for symptom risk more than the daily blue light shirt clip (OR 2.45 vs. 1.62). The area under the receiver operator curve for the blue light wristband dose was 0.78, suggesting 78% predictive accuracy.

Conclusion These data demonstrate that wearable blue light dosimetry worn as a wristband is a promising method for measuring light exposure and predicting and preventing symptoms in EPP.

Keywords
blue light; erythropoietic protoporphyria; light dosimetry; light sensitivity; photosensitivity; protoporphyria; wearable technology.

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Introduction

Photosensitivity disorders are a heterogeneous group of idiopathic, immunologic, or metabolic disorders that include erythropoietic protoporphyria (EPP), solar urticaria, actinic prurigo, polymorphic light eruption, photoaggravated dermatoses, and porphyria cutanea tarda, and these can drastically impair quality of life.[1,2] One severe form of photosensitivity is erythropoietic protoporphyria (EPP).[1,2] Patients with EPP experience prolonged, painful cutaneous photosensitivity caused by the accumulation of the light-sensitive molecule protoporphyrin IX in erythrocytes and plasma.[3–5] The severity of pain experienced by patients with no effective ameliorating therapies once the pain begins often leads patients to over-protect from light, further limiting their quality of life.[2,6–8] Moreover, clinical trials in EPP have been limited by an inability to objectively and accurately track sunlight exposure, and measurement of light sensitivity has relied solely on patient self-reporting of outdoor time.[9] Technologies that enable informed exposure monitoring, coupled with data analysis algorithms for personalized guidance, can be life-changing for individuals with EPP and other photosensitivity disorders by providing quantitative endpoints for clinical trials and guiding patients' light exposure to prevent symptoms, thereby improving quality of life.

This study builds on valuable prior light dosimetry work in EPP and other conditions. Light dosimetry has also been tested in numerous studies of daylight photodynamic therapy, which takes advantage of the protoporphyrin molecules' photosensitive properties to treat actinic keratosis.[10] Light dosimetry has also been used to evaluate photoprotective behavior in xeroderma pigmentosum.[11,12] In EPP patients, prior work by a group in the Netherlands demonstrated that white light dosimetry could detect a treatment effect of afamelanotide, as demonstrated by increased light dose, and they measured significant differences in light dose between EPP patients and controls.[13] Furthermore, a Danish group importantly used blue light dosimetry to quantify light exposure doses in 14 EPP patients, finding higher glove use on days with higher light doses and a negative correlation between daily light dose and patients' erythrocyte protoporphyrin concentration.[14] UV light dose, red light dose, indoor-calibrated blue light dose, and self-reported light exposure were not measured in these prior studies, and correlations between daily light dose and daily symptoms were not reported, which are additional contributions of the current work compared with those prior EPP studies. Our group has previously evaluated UV light dosimetry in EPP patients, demonstrating associations between daily light dose and symptoms, as well as with patients' self-reported degree of light sensitivity.[15,16] However, blue light dose and red light dose were not measured.

The current study utilizes a millimeter-scale, ultralow-power wireless platform for autonomous measurement of electromagnetic radiation (EMR) dosimetry that continuously monitors

wavelengths of interest across the UV–VIS spectrum and pairs with a smartphone application for seamless data collection and analysis (Figure 1a,b).[17,18] The device wavelengths were selected to match the absorbance spectrum of protoporphyrin IX, the molecule responsible for both EPP-related light sensitivity. Phototesting of patients with EPP has supported the importance of the Soret band of blue light (~408 nm) in EPP light sensitivity.[19,20] Because protoporphyrin IX has its primary absorbance peak at the Soret band and smaller peaks in the orange-red spectrum, four sensing channels were designed to measure the instantaneous intensity and cumulative light dose in the spectral ranges of UVA (360–400 nm), orange-red (560–620 nm), and indoor and outdoor blue (390–420 nm) (Figure 1c).[21] Our objective was to develop and validate a wearable light exposure device and correlate measurements with light sensitivity in EPP to predict and prevent symptoms. Our results show significant promise for its use in EPP and suggest promise for other photosensitivity disorders.

Materials and methods

Multichannel light dosimeters for photosensitivity monitoring

An illustrative example (Figure 1a,b) demonstrates the use of wireless light dosimeter devices worn as wristbands and lockets that autonomously measure the dose of exposure to EMR from the sun and indoor lights, then transmit the real-time data at pre-programmed intervals via Bluetooth Low Energy (BLE) protocols to a digital, wireless phone interface for data processing and management. Dimensions are 23 mm for diameter, 3 mm for thickness, and <500 mg for weight. The device was designed and validated as described in a prior manuscript.[18]

Dosimetry study with EPP patients

Five patients with a diagnosis of EPP who were 18 years old or older were recruited from patients who had previously participated in entirely remote EPP research studies through

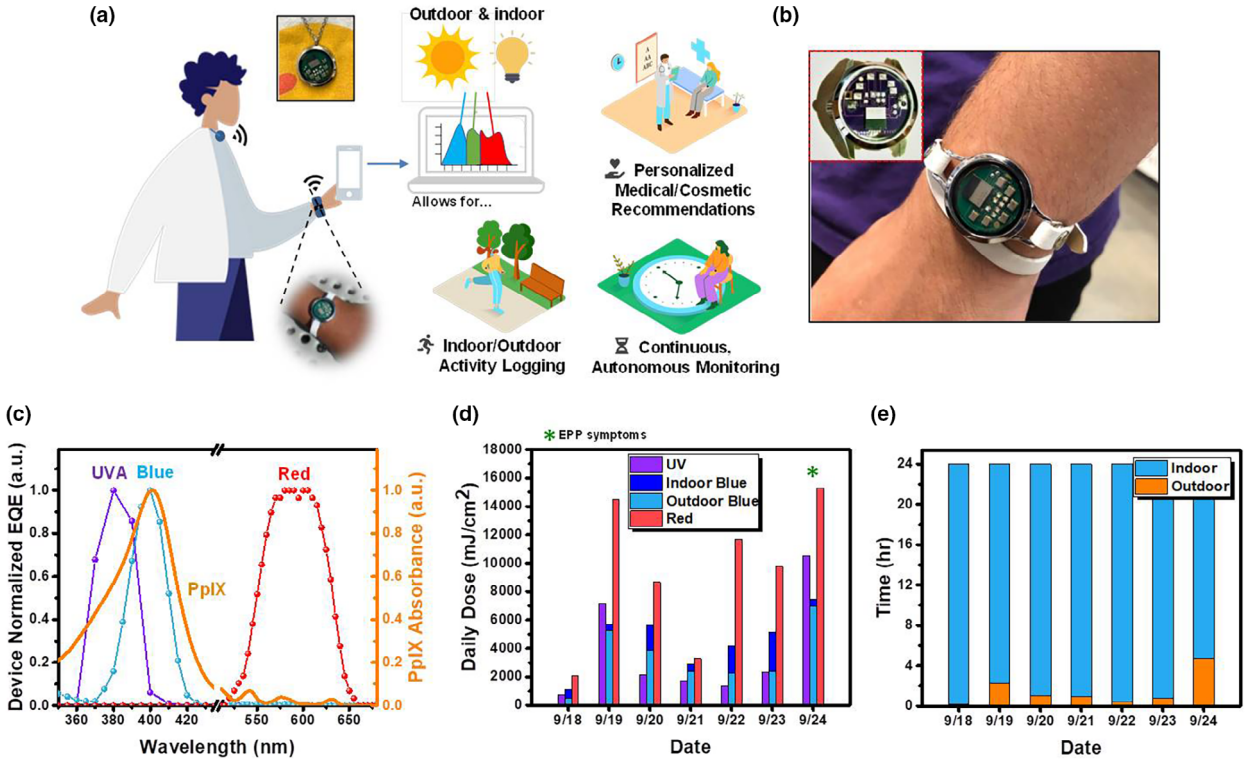

Figure 1 Power-efficient, autonomous multichannel wireless light dosimeter designed for measuring light exposure in EPP. (a) Schematic illustration of wireless light dosimeter with real-time synchronization capabilities for the quantification of indoor/outdoor exposure. (b) Photographs of a wireless light dosimeter encapsulated in a wristband unit. The inset shows a top view of the device with four sensing channels. (c) Absorbance spectrum of the protoporphyrin IX molecule and normalized external quantum efficiency (EQE) spectra of the light dosimeter sensing channels for detecting UVA, blue, and red irradiations. (d) Representative one-week data of total light dose per channel per day for one patient is displayed. For times when UV irradiation is >0.3 mW/cm^2, the outdoor blue dose is reported; for times when UV irradiation is <0.3 mW/cm^2, the indoor blue dose is reported. (e) Representative one-week data for one patient of indoor/outdoor time based on the UV irradiation cutoff of 0.3 mW/cm^2

Massachusetts General Hospital (MGH). The study size was decided based on the results of that study.[15] Study data were collected and managed using the HIPAA-compliant REDCap electronic data capture tools hosted at MGH.[22,23] The Mass General Brigham HealthCare Institutional Review Board approved this study (Protocol 2021P001569). Written informed consent was obtained from the participants before participation in the study.

Participants were enrolled across the United States for this observational pilot study in August 2021, with light exposure measurements occurring between August and October 2021, and all study procedures were completed remotely. First, participants completed a detailed light sensitivity and symptoms survey. Subsequently, subjects completed three separate weeks of light dosimetry and concurrently self-reported outdoor time, with participants reporting start and stop times for each outdoor exposure by text surveys sent through the REDCap/Twilio interface. Participants were blinded to the measured light dose. Throughout the study, each participant wore two devices, one as a wristband/watch on the dominant hand and one as a shirt clip. Participants also completed daily text surveys that assessed the presence of symptoms, time of symptom onset, start and stop times for sun-protective clothing, and type of sun-protective clothing. Throughout, participants were asked to expose themselves to light to the point of mild prodromal symptoms at least weekly, symptoms which could include tingling and pruritus but did not need to include pain. Even mild prodromal symptoms were considered symptoms for the purpose of the analysis.

Analyses were conducted using RStudio software version 3.5.3, with a two-sided $P < 0.05$ being considered significant. Due to the study's small sample size, the analyses were mainly descriptive, and future studies will be needed for validation. To account for the differences in the unit measure of device dose and self-reported outdoor time, values were standardized for comparisons with a mean of zero and a standard deviation (SD) of one. Any days with missing light dosimetry were excluded from the analysis. Generalized estimating equation (GEE) models with an identity link and Gaussian family distribution were performed to determine the association between daily light exposure and symptoms, accounting for within-participant associations. Likewise, GEE models with a logit link and binomial family distribution were used to determine the risk of EPP symptoms associated with light exposure. Model discrimination was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC).

Results

Demographics

Five EPP patients participated in the study with a mean age of 39.2, and 80% were female (Table 1). Three reported no sensitivity to indoor lights. Participants showed excellent compliance with wearing the device and completing daily text message surveys (91.4% and 99% of days, respectively). Two participants lived in California, one in Colorado, one in Missouri, and one in Minnesota.

Table 1 Participant characteristics

	Participant characteristics
Age (years), mean (SD, range)	39.2 (17, 20–65)
Sex, *n* (%)	
Male	1 (20%)
Female	4 (80%)
Self-reported skin tone, mean (SD, range)	3.4 (1, 2–5)
Sensitivity to indoor light, *n* (%)	
Yes	1 (20%)
No	3 (60%)
Only during an EPP phototoxic reaction	1 (20%)
Sunlight exposure time before prodromal symptoms, *n* (%)	
0–10 min	2 (40%)
11–30 min	1 (20%)
31–59 min	1 (20%)
1–3 h	1 (20%)
Participant compliance, mean (range per patient)	
Daily survey completion	99% (95–100%)
Wore the device all day	91.4% (86–100%)
Daily doses, mean (SD, max) mJ/cm^2	
UV dose	11,963 (20,087–93,377)
Blue light dose – outdoor	8,278 (11,947–52,965)
Red light dose	15,450 (18,240–85,065)

EPP, erythropoietic protoporphyria.

Light dose over time

Figure 1d,e and Figure S1 depict representative daily light doses and symptom data per channel for 1 week for one patient. For this data subset, symptoms occurred during the day of greatest light exposure. During the study, the average daily UV dose across patients was 11,963 mJ/cm^2, the average daily outdoor blue light dose was 8,278 mJ/cm^2, and the average daily red light dose was 15,450 mJ/cm^2 (Table 1).

Association between light exposure measurements and symptoms in EPP

Between symptom and non-symptom days, the group difference in light dose was greatest for the blue light watch dose and least for self-reported outdoor time (group difference = 1.06 and $P = 0.001$, group difference = 0.88 and $P < 0.00001$, respectively, Figure 2). A one standard deviation (SD) increase from the mean in daily blue light watch device dose was associated with the largest odds ratio (OR) for EPP symptoms risk (blue channel OR: 2.76, 95% CI: 1.79–4.24, $P < 0.00001$, UV light OR: 2.42, 95% CI: 1.54–3.80, $P = 0.000067$, red light OR: 2.40, 95% CI: 1.61–3.57, $P < 0.00001$, self-report OR: 2.38, 95% CI: 1.60–3.54, $P < 0.00001$, Figure 2). When evaluating the ability of the blue light watch dose to predict EPP symptoms, the area

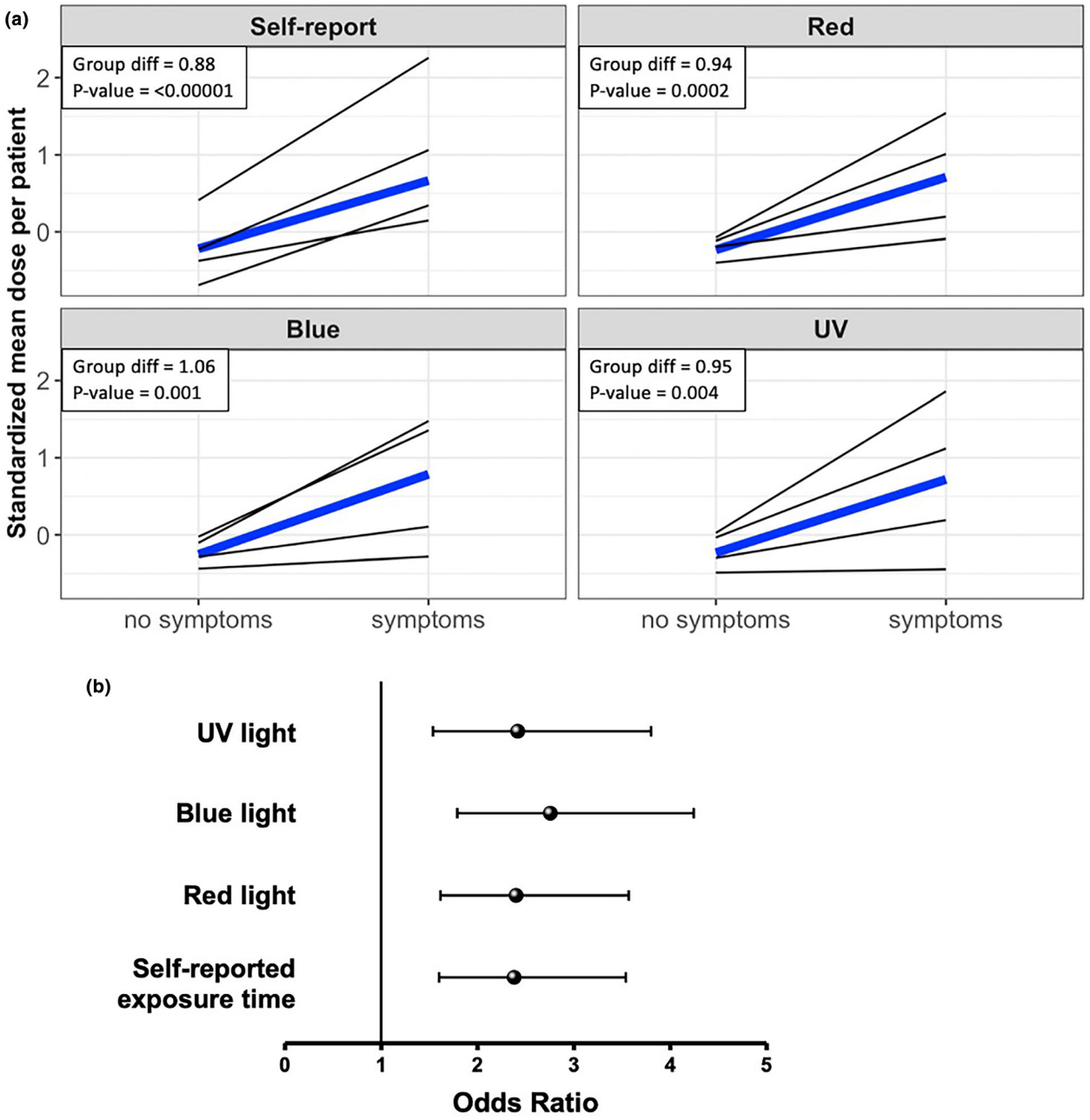

Figure 2 Both watch device doses and outdoor times are associated with EPP symptoms and with an increased odds ratio for symptom risk, but the blue light watch dose has the highest association. Dose and exposure time data were standardized to a mean of 0 and a standard deviation of 1 for comparison. (a) Association with EPP symptoms. The group difference reports the difference between symptomatic and nonsymptomatic days. The mean for one patient is represented as a black line. The blue line is the mean of all the patients. (b) The odds ratio for symptom risk. The odds ratio with a 95% CI is depicted

under the receiver operator curve (ROC AUC) was 0.78, suggesting a 78% predictive accuracy.

We attempted to consider the known efficiencies of various wavelengths for passing through the skin, as specific wavelengths penetrate the skin more efficiently and chromophores block others in the skin.[21,24–27] When utilizing a protoporphyrin-weighted dose incorporating a weighted blue light dose and a weighted red light for the presumed depth of protoporphyrin-light stimulation in EPP, associations with symptoms or symptom risk did not improve. Of note, the blue channel dose was correlated with the UV dose, the red dose, and the outdoor time (Pearson's correlation coefficient 0.97, 0.94, 0.88, $P < 0.00001$ for all).

Doses from clip versus watch for EPP symptoms

When evaluating only days with both complete clip and watch data, the group difference between symptom and non-symptom days was greater for the blue light watch dose as compared with the blue light shirt clip dose (group difference = 1.21 and $P = 0.0001$, group difference = 0.65 and $P = 0.002$, respectively, Figure 3). Similarly, a one standard deviation increase from the mean in the daily blue light watch dose was associated with a larger OR for symptom risk as compared to the daily blue light shirt clip (OR: 2.45, 95% CI: 1.76–3.41, $P = 0.02$ vs. OR 1.62, 95% CI: 1.10–2.40, $P < 0.00001$, Figure 3). Furthermore, the watch design was universally preferred by the patients compared with the shirt clip.

Discussion

In just five patients, this study demonstrates that wireless light dosimetry is at least as valuable as self-reported light exposure and less burdensome for patients. All measured light dosimeter doses and self-reported outdoor times were associated with symptoms and symptom risk. Still, the strongest association was observed with the blue light watch dose because of the engineering advantages of this device, which allow for ease of use and data collection. Because blue light is essential in mood disorders, daylight photodynamic therapy, and other conditions, this device and data may contribute to advancing future studies of light dosimetry in EPP and other conditions affected by EMR radiation.

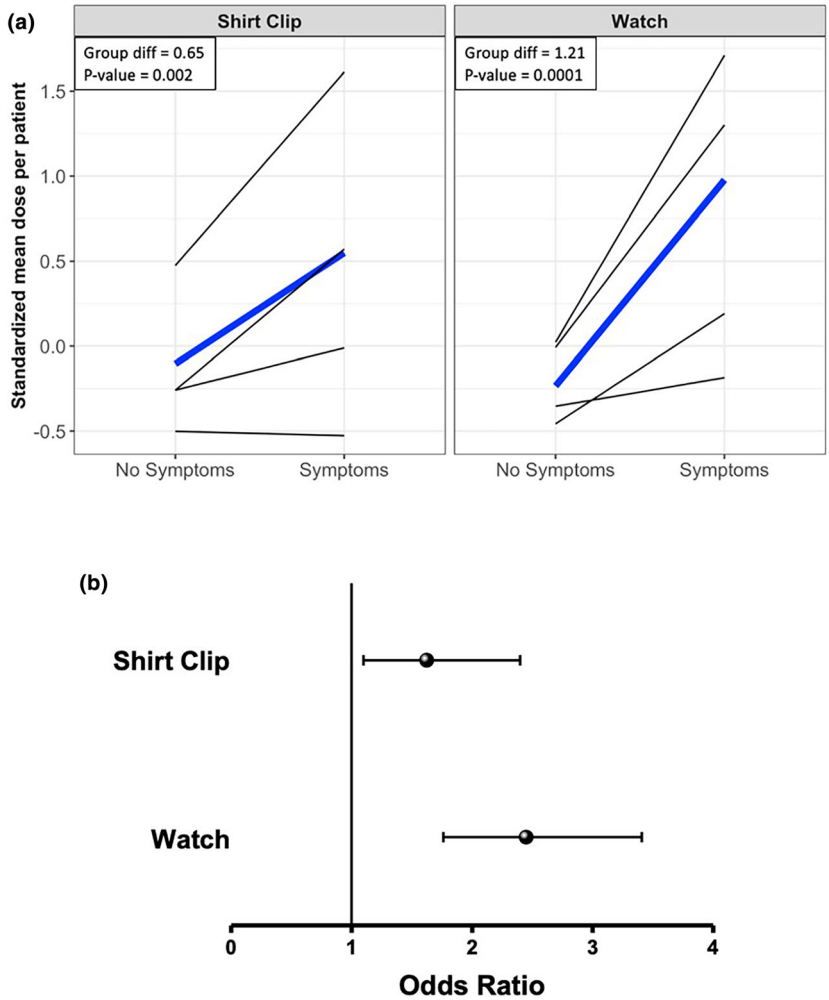

Figure 3 Blue light watch dose has a stronger association with symptoms and a greater odds ratio for symptom risk as compared to the blue light shirt clip dose. Dose and exposure time data standardized to a mean of 0 and SD of 1. (a) Association with EPP symptoms. The group difference reports the difference between symptomatic and nonsymptomatic days. The mean for one patient is represented as a black line. The blue line is the mean of all the patients. (b) The odds ratio for symptom risk. The odds ratio with a 95% confidence interval is depicted

The ROC AUC for the model incorporating the blue light watch dose suggests that blue light watch dosimetry could eventually be used to predict and prevent symptoms in EPP. However, more studies are needed. The study was not statistically powered to discriminate differences in ROC AUCs between light doses and self-reported outdoor time. Self-reporting outdoor time is highly dependent on patient engagement and is burdensome to patients, with the potential for wide variability in the accuracy of reporting between patients. Notably, the patients recruited for this study had already been known to have high reliability for self-reporting light exposure from a prior study, so self-report compliance may have been higher than the broader patient population.[16] Although only five patients participated in the study, each had up to 21 days of light exposure and a daily possibility for symptoms.

While the watch performed better than the shirt clip in EPP patients, as determined by the higher OR for symptom risk and the universal preference for the watch, this might not be true in those without EPP or those with photosensitivities other than EPP. The watch captures light that most closely approximates the light doses on EPP patients' most sensitive skin region: the hands.[16] Furthermore, the OR for symptom risk was highest for the blue light channel, consistent with what was expected based on the protoporphyrin absorption spectrum (Figure 1c).

The device used in this study offers several notable advantages over traditional UV light dosimeters, as this device has the capacity to measure indoor blue light, outdoor blue light, and red light, allowing for broader uses for conditions with heightened sensitivity to these additional wavelengths. Compared with traditional indicators of photodegraded polymers, the device excels in its ability to calculate changes in risk due to other factors, such as the prior days' exposure or latitude and longitude, if deemed necessary for particular medical conditions. Such capabilities become particularly crucial in EPP, as patients' light sensitivity increases markedly in the days following increased light exposure.[15,16] Moreover, the device can directly communicate risks to patients through a cellphone application and send data to researchers and physicians to analyze temporal patterns in doses and symptoms.

This study's limitations include the relatively small number of patients in one disease type and the inability to account for the use of protective clothing fully. Because participants were asked to expose themselves to light to the point of prodromal symptoms at least weekly, the data might not represent their typical light exposure practices. Notably, one participant had no symptoms for days without missing data during the study, accounting for four black lines in Figures 2 and 3. Despite these limitations, the blue light watch dose emerged as the most effective metric, indicating that blue light watch dosimetry should be used in future clinical studies and clinical trials rather than conventional self-reported approaches.

Future studies are needed to develop and validate prediction models that would be able to warn patients about their symptom risk, as well as device/app pairs that can be used in EPP, other photosensitivity disorders, and photodynamic therapy, as well as for the regulation of mood, sleep, and skin health.[21,24,26,28,29] For EPP specifically, this study lays essential groundwork for future studies of EPP light dosimetry, which will be critical for clinical trial endpoints and predicting and preventing EPP symptoms.

Acknowledgment

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Supporting Information

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

Figure S1. Time series light dosimetry data. Photograph of the encapsulated wireless light dosimeter in a wristband unit (upper left) and the reported UV index (upper right) on Oct 2nd, 2021, in Santa Monica, CA (source: NOAA, National Weather Service). Time series data, from top to bottom: wireless readout of V_{sc} data for (1) the indoor blue channel and (2) outdoor UV, red, and blue channels, (3) derived exposure intensities, and (4) cumulative exposure doses. Orange background and labels stand for self-reported outdoor time. Green labels represent the outdoor time as determined by the wireless light dosimeter according to the pre-determined UV intensity cutoff. During outdoor exposure, as determined by the UV intensity cutoff, the calculated intensity and cumulative dose for the indoor blue channel are set to zero. The intensity and dose data for the indoor blue channel (blue line) are magnified 10-fold for ease of data visualization.