Patient Related Outcome Measures

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ORIGINAL RESEARCH

Development and Content Validation of Novel Patient-Reported Outcome Measures to Assess Disease Severity and Change in Patients with Erythropoietic Protoporphyria: The EPP Impact Questionnaire (EPIQ)

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Purpose: Erythropoietic protoporphyria (EPP), a rare inherited disorder, presents in early childhood with severe, painful phototoxicity, with significant impacts on health-related quality of life (HRQoL). Previous studies have not captured all concepts important to patients. Therefore, this study sought to develop a novel, comprehensive, and content valid patient-reported outcome (PRO) measure to assess the efficacy of new therapies.

Patients and Methods: Qualitative interviews were conducted with EPP participants and clinical experts to obtain views on concepts relevant to patients. Results informed the development of novel PROs, which were debriefed during subsequent combined concept elicitation and cognitive debriefing interviews.

Results: Twenty-three interviews were conducted with 17 adults and 6 adolescents with EPP. Concept elicitation revealed that participants experienced many symptoms with significant variability. The most common were burning, pain, swelling, and tingling. Tingling was the most common prodromal symptom, while burning was the most bothersome, and pain was the worst full reaction symptom. Participants reported being negatively impacted in their ability to do daily activities, and social and emotional functioning. Many reported impacted ability to work and be productive at their job. Participants reviewed and completed the newly developed PRO measures assessing full reactions and ability to do activities, as well as items to assess severity and change in severity of prodromal symptoms, full reactions, and EPP overall. All measures were found to be comprehensive, clear, and relevant.

Conclusion: PRO measures are needed to assess important aspects of HRQoL and evaluate therapeutic response. These PRO measures are unique in assessing overall severity and change in EPP.

Plain Language Summary: Erythropoietic protoporphyria (EPP) is a rare but severe condition; people with it experience painful reactions on their skin after exposure to sun and in some cases, artificial light. Measuring how EPP affects individual's lives is critical to properly understanding the disorder. However, current questionnaires do not capture all the issues important to individuals with EPP. Therefore, we conducted interviews with individuals with EPP and doctors who are experts in EPP to create and evaluate a questionnaire that addresses these gaps. The interviews showed that people with EPP experience many symptoms with lots of variability, and that EPP impacts their ability to work and be productive at their job. This information was used to create a questionnaire that measures individual's full EPP reactions and ability to do activities (EPP Impact Questionnaire), and how bad early warning symptoms, full reactions, and EPP overall are, as well as how they change (Patient Global Impression of Severity and Change). The questionnaire was found to be clear and relevant. This is important in being able to measure how patients feel and function and whether treatments work for people with EPP.

Keywords: erythropoietic protoporphyria, porphyria, patient-reported outcome development, qualitative interviews, rare disease

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Introduction

Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are rare, inherited inborn errors of heme metabolism that present with childhood-onset, severe, painful phototoxicity.[1,2] Collectively these are both referred to as EPP. Additional complications can include anemia, cholelithiasis, liver dysfunction, and psychosocial issues.[1,3,4] The diagnosis of EPP is often delayed, with one study reporting 13 years as the mean time between initial symptoms and diagnosis.[5]

Symptoms after sun exposure typically include tingling, burning, and/or itching that may progress rapidly to severe pain, erythema, and swelling, usually on the face and dorsum of the hands, and any exposed areas.[1,2] In some cases, symptoms may also develop due to artificial light.[6] Prevalence estimates based on individuals entering the health care system range from 1 in 75,000 to 1 in 200,000 individuals,[7] however genetic data from the UK Biobank estimates pathogenic variants causing EPP are found in approximately 1 in 25,000 individuals, suggesting EPP is underdiagnosed.[8] Although sun exposure tolerance and time to symptom resolution are highly variable, many individuals can only tolerate less than 30 minutes of sun exposure before onset of prodromal symptoms. Pain can be excruciating, and many individuals do not experience adequate pain relief from analgesics, including opioids.[1] In addition, severe phototoxic reactions can last for several days[1–4,7.]

There is only one approved treatment for adults with EPP in the US, European Union, and Australia, afamelanotide, a subcutaneously administered α-melanocyte stimulating hormone analogue.[9] Nevertheless, the mainstay of management continues to be sun protection and avoidance of sunlight for individuals in which afamelanotide is not an option (pediatric patients, access issues for adult patients, etc.).

Because of the need to avoid sunlight as much as possible for fear of severe phototoxic reactions, EPP can have a significant impact on daily life[4,10–13] and health-related quality of life (HRQoL). This has been demonstrated in several studies using generic and EPP-specific patient-reported outcome (PRO) measures.[4,13–16] However, the content of these currently available PRO measures is limited, and they do not capture all the relevant concepts important to individuals with EPP. For instance, generic PRO measures that have been used in studies of dermatologic conditions typically focus on significant visible symptoms, which may not be relevant to EPP. Although the Dermatology Life Quality Index (DLQI), a common PRO instrument in many dermatology studies, was used in several studies of EPP,[4,12,17,18] it was not sensitive to changes in response to treatment.[9] Previous studies have also utilized the PROMIS-57, Hospital Anxiety and Depression Scale, and Illness Perception Questionnaire in EPP patients. Of these measures, the PROMIS-57 had the highest correlation with clinical features of EPP, specifically, the physical function, pain interference, and satisfaction with social roles domains.[19] However, a recent trial of dersimelagon, an oral melanocortin 1 receptor agonist, showed it was not sensitive to changes in response to treatment, although scores in the physical function domain and pain intensity did appear to improve.[20]

One EPP-specific measure referred to as the "EPP-QoL" was specifically developed for use in clinical trials with afamelanotide to assess long-term effects of treatment.[15,16,21,22] However, the "EPP-QoL" was developed without patient input as is recommended by current standards and regulatory guidance,[23,24] and it lacks a robust assessment of well-being.[25] Validation studies of the "EPP-QoL" showed that the well-being domain had poor psychometric properties and was removed from the final questionnaire, resulting in only a unidimensional "EPP Symptom" score.[25] It is also a proprietary tool, which limits its use. Furthermore, although the "EPP-QoL" generally showed EPP negatively impacts daily activities, it was not found to be very specific to clinical features of EPP,[19] and does not specifically assess severe pain, avoidance of sunlight, or how these behaviors impact daily life. Therefore, new PRO measures developed with direct patient input are still required for this population.

Additional PROs have recently been proposed as useful endpoints in clinical trials, specifically measuring time-to-prodrome (TTP), and the amount of time a patient can be in direct sunlight before experiencing prodromal, or early warning symptoms.[26] This is useful in quantifying sun exposure and for not putting the patient at significant risk for a severe phototoxic reaction. However, these outcomes do not take into account symptom severity, and the concept of prodromal symptoms in EPP requires further study.

Having a content valid, reliable, and responsive measure of these PROs for use in this population is important, not only for accurately characterizing EPP patients' well-being, but also for assessing the efficacy of potential new therapies.

Therefore, the goal of this current research was to conduct in-depth, qualitative interviews with adults and adolescents with EPP in order to develop a novel, comprehensive, and content valid PRO measure.

Materials and Methods

Data collection for this qualitative interview study was conducted from March 2022 to June 2022. Approval for the study was provided by an independent Institutional Review Board, WCG IRB.

Recruitment

Potential participants were referred from the United Porphyrias Association (https://www.porphyria.org). Once their interest was confirmed, potential participants were screened for eligibility. Participants aged 12 to 17 signed the Assent Form, while their parent signed the Parental Permission Form. Adult participants signed an Informed Consent Form. Participants' assent or informed consent included publication of anonymized responses. The study was approved by an institutional review board (WCG IRB) and conducted in accordance with the Declaration of Helsinki. The target sample size was 20 participants to attain saturation.

Participants

Inclusion criteria included participants >12 years of age, having a written confirmed diagnosis of EPP (via a physician's letter, genetic testing results, or chart note), and living in the US or Canada. If participants were currently receiving afamelanotide, they must have initiated treatment within the last three months to ensure they still had sufficient recall of their pre-treatment symptoms. Participants were excluded if they were currently enrolled in a clinical trial or had a medical or psychiatric condition (or treatment for condition) that resulted in a cognitive or other (visual, hearing) impairment that could potentially interfere with participating in this current study. Other methods of sun protection (ie, beta-carotene, sunscreens, etc.) were not considered exclusionary as they are not considered effective treatments for EPP. Participants completed a background questionnaire containing demographic and clinical information prior to their interview. After completing the questionnaire and interview, participants received a $150 Amazon gift card as compensation for their time.

Interviews

Interviews were conducted with individuals with EPP, as well as five clinical experts that treat EPP, who were asked to provide their opinions on concepts relevant to individuals with EPP. Input from clinical experts were primarily used in developing a Sunlight Exposure Diary described elsewhere[27] and used to inform the development of the interview guide in this current study. Interviews were done using semi-structured interview guides (one for individuals with EPP and one for clinical experts), developed specifically for this research. The first 5 patient interviews included open-ended concept elicitation questions only. Results from those interviews were used to inform the development of draft questions for the EPP Impact Questionnaire (EPIQ) that was debriefed during the subsequent interviews that used a combined concept elicitation portion (CE) and cognitive debriefing (CD) approach. Due to time constraints, not every question was asked of all participants. The purpose of the CD portion of the interview was to determine whether the PRO measure content, clarity, and relevance to patients was adequate. Due to the COVID-19 pandemic, to ensure the safety of participants, all interviews were conducted over Zoom by an experienced health service researcher. Zoom allowed the interviewer and the participant to see one another through the video camera. In addition, the interviewer was able to share her screen to display the items, so that participants could complete the questionnaires in real-time, while answering questions about each item. All interviews were recorded and transcribed, and reviewed for accuracy for analysis purposes.

Analysis

A coding dictionary was developed to organize and categorize concepts of interest from the interview transcripts and included descriptions and examples for each code to ensure consistency across coders. Each transcript was coded by one coder, and then reviewed, summarized, and analyzed by a second coder. Saturation tables were developed to categorize each symptom mentioned by each participant. Interviews were conducted in waves so that, as necessary, revisions could be made iteratively to the newly developed PRO measures based on results from the interviews.

Results

Participant Characteristics

Twenty-three participants were enrolled, including 17 adults and six adolescents. There were approximately equal numbers of males and females, and the majority of participants were White (94%). Most adults had a college degree or higher (71%) and worked full-time for pay (71%). The average age of the adults was 40 years. Most were not on treatment currently, although 2 adults (9% of all participants) were currently receiving afamelanotide. Six adults (26% of all participants) had received afamelanotide previously. Co-morbid conditions were fairly common, with liver disease (29%), anemia (24%), and gallstones (29%) most common. The average age of adolescents was 14 years of age (median: 13.5; range: 12–15 years of age). Most adolescents (67%) were currently taking beta-carotene. Additional details are provided in Table 1.

Table 1 Participant Characteristics

	Adults (n=17)	**Adolescents (n=6)**
Duration of Disease (mo) (median, IQR)	286, 288	83, 31
Disease type		
EPP	15 (88)	6 (100)
XLP	1 (6)	0
Unknown	1 (6)	0
Protoporphyrin levels		
Known	10 (59)	2 (33)
Reported levels (mcg/dl) (mean ± SD)	2112 ± 1661	283 ± 371
Unsure	7 (41)	4 (67)
Other comorbid conditions, n (%)		
Liver disease (type not specified)	5 (29)	0
Anemia	4 (24)	1 (17)
Gallstones	5 (29)	0
Other	3 (18)	2 (33)
None	10 (59)	4 (67)
Gender, n (%)		
Male	9 (53)	3 (50)
Female	8 (47)	3 (50)
Age, yr (mean ± SD) (range)	40 ± 14 (20–61)	14 ± 1 (12–15)
Education, n (%)		
Less than HS	0	6 (100)
HS diploma	2 (12)	0
Some college	3 (18)	0
College degree	10 (59)	0
Professional or advanced degree	2 (12)	0
Ethnicity, n (%)		
Hispanic or Latino	2 (12)	0
Non-Hispanic or Latino	15 (88)	6 (100)
Race, n (%)		
White	16 (94)	6 (100)
Asian	1(6)	0

(*Continued*)

Table 1 (Continued).

	Adults (n=17)	Adolescents (n=6)
Marital status, n (%)		
Married	7 (41)	0
Living with partner	4 (24)	0
Widowed/divorced/separated	2 (12)	0
Single, never married	4 (24)	6 (100)
Household Income, n (%)		
< $25,000	1 (6)	0
$25,000 - $49,999	3 (18)	0
$50,000 - $74,999	3 (18)	0
$75,000 - $99,999	1 (6)	1 (17)
> $100,000	7 (41)	3 (50)
Decline to answer	2 (12)	2 (33)
Work status, n (%)		
Full time	12 (71)	0
Part time	1 (6)	0
Unemployed due to EPP	1 (6)	0
Unemployed unrelated to EPP	0	0
Unemployed, reason unknown	1 (6)	0
Student	2 (12)	6 (100)
Treatment for EPP, n (%)		
a. Scenesse (afamelanotide)	8 (47)	0
Currently taking	1 (13)	
b. Beta-carotene (solatene)	4 (24)	3 (50)
Currently taking	0	2 (67)
c. Oral cysteine	1 (6)	0
Currently taking	0	
d. Cholestyramine	4 (24)	0
Currently taking	0	
e. Ursodeoxycholic acid	1 (6)	0
Currently taking	1 (100)	
f. Cimetidine	0	1 (17)
Currently taking	0	1 (100)
g. Other	3* (18)	2** (33)
Currently taking	0	2 (100)

Notes: *Previously enrolled in dersimelagon clinical trial. **Vitamin A, pain medication.

Concept Elicitation

Concept elicitation revealed the following results, and are also summarized in Table 2.

Living with EPP

Participants were asked what it is like to live with EPP. Several participants (n=6) said that it is something always on their mind, and they constantly need to be aware of their sun exposure. Some adult participants (n=4) referenced how difficult it was as a child (Table 2).

Time in Direct Sunlight

Participants were asked how much time they spend outside in direct sunlight each day. Estimates varied, and responses ranged from 1 minute to two to three hours. Forty-one percent of participants (n=7 of 17) said symptoms occur after less

Table 2 Illustrative Quotes from Concept Elicitation Interviews

Topic	Illustrative Quotes
Living with EPP	Participant 001–008A: Well, so, as a kid, I'd say it was very lonely and very challenging because I'd see all my classmates, all my teammates like playing outside and not really caring about the sun or worrying about their safety and being out there. Meanwhile, if I was outside, I'd always be like monitoring, okay, I can get this amount of time in the sun at this time, I get this amount of time in the sun at this time or else I am going to be in a lot of pain. A lot of times, because I played outdoor sports as a kid, as well, and so I'd end up sacrificing either my health and just going out and playing.
Outdoor Activities	Participant 001–001A: I really don't do much outdoors. I pretty much stay inside for the most part. Participant 001–001AD: Well, usually in the summer, I go out and like bike around with my friends on the bikes and stuff like that, but usually if I have like good sunscreen on and like SPF clothing, then I am usually okay just as long as I do not get in the sun as much as I should.
Symptoms- Location of Symptoms Fifty-nine percent of participants (n=10 of 17) said they experience symptoms wherever their skin was exposed. Forty-one percent of participants (n=7) typically experience symptoms on their hands, feet, and face.	Participant 001–016A: Nose, ears. I mean I am bald, so my head. You know that's a whole other precaution not to take these days. Predominantly exposed skin. Ankles, tops of feet, hands. You know I tend to drive with my hands upside down like this, you know. Chase shadows around the car with the steering wheel, but it's exposed skin.
Symptoms- Seasonal Effects Ninety-one percent of participants (n=10 or 11) agreed that their symptoms vary depending on the season.	Participant 001–003A: Yeah, so I would say, because I grew up in [_]. In [_] they were better in fall and winter. Spring and summer are the worst. If you are in Colorado, it's sunny 300 days a year and even when there is snow, like when you are hiking, that reflection off the snow can be kind of tough. So, now it's not really any different. I suppose it's easier, but even our winters. Like it's supposed to be 78 this week. So, you can bundle up. Like in Minnesota I can bundle up more. So, winters were better because I was bundled up. If I would just go stand out in the sun and the snow, I'd just, I'd get as many sun reactions.
Symptoms- Time of Day All participants asked (n=6) agreed that their symptoms vary based on the time of day of the exposure. Eighty-six percent of participants (n=5 of 6) said mid-day they are most at risk, while 17% (n=1) said late afternoon is the worst time of day.	Participant 001–012A: Well, in my case, that is still considering mild. I am able to do a lot of activities outdoors, but I have to restrict the time that I stay outdoors between 11 and 3:00. Those are very dangerous hours for me, the time I will be outside more, let us say 20 minutes, 25 minutes in the sun because I will start feeling the pain.
Symptoms - Onset	Participant 001–001A: I really do not do much outdoors. I pretty much stay inside for the most part. I used to garden, but I stopped doing a lot of things outdoors, I'd say, in the last ten years. For me, my EPP seems worse, seems more instant. Over time, it's just, it's faster. The reactions are faster. I do not have much leeway to sort of go out and enjoy anything outside.
Symptoms- Prodrome Participants were asked if they typically experience symptoms the first time they go out in the sun or whether they need multiple exposures. Sixty percent of participants (n=6 of 10) said they experience symptoms the first time they are exposed to sun, while 40% (n=4) said they sometimes will not experience symptoms during the first exposure, but will experience the symptoms the next day after another exposure (ie, priming effect).	Participant 001–011: No, it's probably like, it's just a constant. So, I mean like right now, until probably November, December, like any time I go step outside, I will be burning. So, you feel the tingling and then, bam, seconds later you are burning. So, it's just like a constant, it's just constant for me. Participant 001–010A: If I was already, like today I am already burnt. Like today has actually been kind of rainy and really cloudy. I was just outside with no gloves on at all and I was fine. Yeah, it's the same thing, though. It tacks on to the next day. So, if I am burnt today and today was really sunny and I go outside, within a few minutes, I mean if not probably even quicker than yesterday I would feel it and I would know like, uh-oh, you know early on. Like as soon as I step outside, I would know. I mean early is not even a word. It's like instant warning, you know what I mean.

(*Continued*)

Table 2 (Continued).

Topic	Illustrative Quotes
Symptom Impacts- Work Impacts	Participant 001–003A: So, again, when I was working on campus, so I'd have to get there early because I'd have to make sure I know where the windows are and where the sun, because if it was a room I was familiar with, I'd know enough to get there early because I want to get my spot, because I did not tell anybody I had it until, I do not know, about seven years ago.
Symptom Impacts- Social Impacts	Participant 001–006A: Can I go out on a boat for a really long time without being protected? No. Will I be uncomfortable if I choose to go and be completely covered? Yes. I will be uncomfortable, but if the group, as a whole, wants to go out on a boat, I do not feel that they should not go on a boat because of me. I will adjust to them, but, yes, it does, socially it does kind of hold you back in some ways. Like I said, I cannot go and lay on a beach like everyone else does or I cannot walk the beach on a hot sunny day without protection. Like I just cannot do it. Participant 001–001A: Well, definitely socially because, you know, I don't, you know I don't do a lot of things, you know invitations or things that people want to do, you know, I won't go do them, you know.
Symptom Impacts- Physical Functioning	Participant 001–006A: Well, it does like when you are, when I have the pain, I also have the swelling. So, when I have the pain and the swelling, obviously, it does affect my fingers, you know my fine motor skills. It would impact just my doing the dishes because that's the hot water. Taking a shower, washing your hands after using the restroom.

than 10 minutes of sun exposure. Forty-seven percent of participants (n=8) said symptoms occur within 10 and 60 minutes of sun exposure.

Symptoms

Participants were asked to describe what symptoms they have ever experienced as a result of EPP. The most common symptoms mentioned spontaneously included burning (91%), pain (74%), swelling (70%), tingling (65%), itching (57%), sensitivity to touch (43%), warmth/heat sensation (39%), blisters (35%), redness/discoloration (30%), and sensitivity to hot/cold (30%) (Table 3). While there was considerable overlap between burning and pain, not everyone that reported burning reported pain, and not everyone that reported pain reported burning. Specifically four participants that reported burning did not report pain, and one individual that reported pain did not report burning. Other concepts that were discussed included symptom causes, frequency, severity, locations, seasonality, time of day, what alleviates symptoms, most bothersome symptoms, and prodrome, which are summarized below and in Table 2.

Exposures Causing Symptoms

Sixty-three percent of participants (n=5 of 8) said they experience symptoms from both sunlight and indirect sunlight, (through windows and reflections), as well as artificial light (ie, from computer screens, indoor lighting), while 38% (n=3) only experience symptoms from sunlight.

Frequency and Severity of Symptoms

Participants were asked if their symptoms vary from day-to-day or whether they are fairly consistent. Sixty-three percent of participants (n=10 of 16) said their symptoms are fairly consistent, while 31% (n=5 of 16) said the symptoms vary. Nineteen percent (n=3 of 16) said that over time as they have gotten older, there was a more rapid onset of symptoms, which were also more intense. Specifically, they have less leeway when outdoors before the onset of symptoms. Two participants mentioned that they only have discoloration, blisters, or burst blood vessels when they are having a severe reaction, indicating that the frequency of these symptoms varies depending on the severity of the reaction. All participants who were asked (n=20) said the severity of their symptoms depends on duration in sunlight or exposure to indirect light.

Table 3 Saturation Grid of Spontaneously Reported Symptoms

	002	005	001	006	003	010	001*	009	011	004	008	013	002*	015	012	014	016	004*	006*	005*	018	017	007*	Frequency % (n)
Blisters	X	X	X	X				X		X								X					X	35% (n=8 of 23)
Burning	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		91% (n=21 of 23)
Headaches									X	X														9% (n=2 of 23)
Hives				X		X																		9% (n=2 of 23)
Itching	X		X	X	X	X					X	X	X			X	X	X		X			X	57% (n=13 of 23)
Leathery/ alligator skin			X												X									9% (n=2 of 23)
Joint pain										X														4% (n=1 of 23)
Nausea						X				X														9% (n=2 of 23)
Numbness		X				X																		9% (n=2 of 23)
Pain	X	X	X	X	X	X			X	X	X	X		X	X		X		X	X	X		X	74% (n=17 of 23)
Pins and needles feeling						X					X				X									13% (n=3 of 23)
Purple /dark dots on skin, broken blood vessels	X	X			X				X							X								22% (n=5 of 23)
Redness/ discoloration		X	X			X						X	X		X					X				30% (n=7 of 23)
Sensitivity to hot and cold	X				X	X				X	X	X					X							30% (n=7 of 23)
Sensitivity to touch	X						X		X	X				X	X	X	X			X		X		43% (n=10 of 23)
Stinging	X								X			X	X								X			22% (n=5 of 23)
Stomach cramps/ upset stomach									X										X					9% (n=2 of 23)
Swelling	X	X		X	X	X	X			X	X		X	X	X	X	X		X	X			X	70% (n=16 of 23)
Tightness									X															4% (n=1 of 23)
Tingling	X		X	X	X		X	X	X	X	X	X	X			X	X	X	X					65% (n=15 of 23)
Warmth/ heat sensation	X			X	X	X	X				X	X			X						X			39% (n=9 of 23)

Notes: *Adolescent participant. Yellow highlighted= First time symptom mentioned spontaneously. Saturation reached by the 11th interview.

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What Helps with Symptoms

Participants were asked if there are things that help their symptoms or when their symptoms are not as bothersome. Forty-three percent of participants (n=6 of 14) said wearing sunscreen and protective clothing minimized symptoms and 43% (n=6 of 14) said using cold wash cloths/ice packs or taking a cold bath helped alleviate symptoms. The use of a fan, going indoors, and taking Advil or ibuprofen also was helpful (Supplementary Figure 1).

Most Bothersome Symptom

Participants were asked what they felt their most bothersome symptom was, regardless of whether it was a prodromal or full reaction symptom. Sixty-nine percent of participants (n=11 of 16) reported that burning was the most bothersome symptom, followed by itching (43%), pain (38%), tingling (19%), sensitivity to hot and cold (19%), and swelling (19%). Burning is often typically experienced as an early warning symptom. When asked about the worst symptom of a reaction, 80% (n=12 of 15) reported pain.

Early Warning Symptoms (Prodrome)

All participants asked (n=21) reported experiencing early warning symptoms. The most common early warning symptoms reported were tingling (75%), itching (25%), burning (25%), sensitivity to touch (20%), sensitivity to hot/cold (20%), and a warmth sensation (20%) (Table 3).

Participants were asked how long they could be in sunlight before they started experiencing early warning symptoms. Responses varied and ranged from 1 minute to two to three hours, with forty-one percent of participants (n=7 of 17) stating symptoms occur after less than 10 minutes of sun exposure. Participants were also asked how long they would avoid the sun after experiencing early warning symptoms. Responses varied and ranged from 20 minutes to several days or until their symptoms went away.

Symptom Impacts

Concepts discussed included daily activities, physical functioning, work impacts, social impacts, and emotional impacts. These are summarized below and in Table 2.

Daily Impacts

The most common impacts reported included not being able to participate in outdoor recreational activities (eg, go to the beach/pool) (n=6 of 14), being unable to sleep primarily due to pain (n=5), not being able to leave the house (n=4), and impacts related to driving (n=3). Several other daily impacts were mentioned by individual participants such as "hanging out with friends" and not being able to do housework. Of those asked, 80% (n=4 of 5) said their physical functioning is not impacted due to EPP. Of those asked, 80% (n=4 of 5) stated that EPP impacts their ability to work. One participant stated that she is not impacted because she is able to work from home and not leave her house.

Four participants who were asked said having EPP impacts their social life. For example, they may not be able to attend a social event because of the location (beach, picnic in the sun) or they might need to leave early to avoid the sun. Participants (n=11) were asked how, if at all, they are impacted emotionally due to EPP. Thirty-six percent of participants (n=4 of 11) reported feeling anxious, 18% (n=2) were depressed, and 18% (n=2) felt isolated and alone (Supplementary Figure 2).

Cognitive Debriefing of New PROs

The measures were debriefed in 9 waves, with revisions made after each wave of interviews. Sample PRO items are contained in Tables 4 and 5.

EPP Impact Questionnaire (EPIQ)

The questionnaire includes a total of 10 items of which 7 assess sun exposure, specifically overall time in the sun, TTP, time to a full reaction, time to improvement of symptoms, and time to full resolution of symptoms. Assessing sun exposure includes both direct and indirect sunlight at the suggestion of the participants, with indirect exposure capturing scenarios like sun coming through a window of a car or home, reflected off of surfaces, etc. Indirect sunlight does not

Table 4 Summary of Cognitive Debriefing of New EPP PRO Draft

Question	Paraphrase Correctly?	Easy or Difficult to Think About?	Clear?	Unclear/Suggested Revisions
On a typical day, **HOW MUCH TIME** were you able to be in sunlight (direct or indirect) **BEFORE** you started having **any early warning symptoms?** _____ minutes	100% (n=8)	78% (n=7 of 9) – easy to think about	33% (n=3 of 9) - clear	44% (n=4 of 9) – would not use the past 7 days, but would ask about time on average/typical day 22% (n=2) – would add an example to show how to add up minutes through the day [Note: the question was omitted from the EPP Questionnaire as information about time until early warning symptoms was now captured in the Diary.]
Once you started having a full reaction, approximately HOW LONG did it take for the FULL REACTION to start to improve? _____ hours OR _____days	100% (n=9)	82% (n=9 of 11) – easy to think about	92% (n=11 of 12) - clear	Two participants would omit minutes as a response option for this item, since reactions typically take days to go away
In the past 7 days, how much did having EPP impact your **ability to do the things you want to do**? □ Not at all □ A little bit □ Somewhat □ Quite a bit □ Very much	92% (n=11 of 12)	Not asked	83% (n=10 of 12) - clear	One participant would clarify whether this includes doing things you want, but wearing protective clothing One participant would clarify if you should respond thinking about whether you have symptoms or not
In the past 7 days, how much did having EPP impact your **overall quality of life**? □ Not at all □ A little bit □ Somewhat □ Quite a bit □ Very much	100% (n=12)	Not asked	92% (n=11 of 12) - clear	One participant would clarify if you should respond thinking about whether you have symptoms or not

include being outdoors in the shade. The EPIQ also includes 3 single items that assess the impact of EPP on ability to perform activities, the impact of EPP on overall health-related quality of life (HRQL), and the comparison of HRQL to those without EPP.

Most participants were able to correctly paraphrase the questions in the EPIQ measure (86–100% of items). Further, participants were able to distinguish between pain and burning. Participants found items to be clear (75–100% of items), with some exceptions. When asked "How much time were you able to be in sunlight before having early warning symptoms?", a few participants suggested to not use the past 7 days, but instead ask about an average/typical day (this change was implemented). Table 4 provides sample items from the questionnaire and summarizes the revisions made based on results from the CD portion of the interview.

As part of the EPIQ, Patient Global Impression of Severity (PGI-S) items assess severity of full reactions, severity of prodromal (early warning) symptoms, and severity of EPP overall. Patient Global Impression of Change (PGI-C) items assessed change in severity of full reactions, change in severity of prodromal symptoms, change in EPP overall, change in TTP, and change in time to a full reaction.

Table 5 Meaningful Change on PGI-S and PGI-C

Items	What Would be a Meaningful Change?
PGI-S [Note: participants provided what they would consider a meaningful change for all PGI-S items instead of each specific item.] 1. Overall, how severe were your **full reactions** in the past 7 days? □ I did not have any full reactions □ Mild □ Moderate □ Severe □ Very severe 2. Overall, how severe were your **early warning symptoms** in the past 7 days? □ I did not have any early warning symptoms □ Mild □ Moderate □ Severe □ Very severe	42% (n=5 of 12) –at least "a little bit better" 25% (n=3) - "much better" 17% (n=2) – "much better" or "a little better" 8% (n=1) – "much better" for question 1 (full reactions); less change would be needed for question 2 (early warning symptoms) 8% (n=1) – "much better" for question 1 (full reactions)
PGI-C [Note: participants provided what they would consider a meaningful change for all PGI-C items instead of each specific item.] 1. How much time are you able to **now** spend in sunlight (direct or indirect) **without** having **early warning symptoms compared to the start of the study**? □ Much more time □ More time □ A little more time □ Same amount of time □ A little less time □ Less time □ Much less time 2. How much time are you able to **now** spend in sunlight (direct or indirect) **without** having **a full reaction compared to the start of the study**? □ Much more time □ More time □ A little more time □ Same amount of time □ A little less time □ Less time □ Much less time	27% (n=4 of 11) – "much more time" 18% (n=2 of 11) – "more time" or "much more time" 18% (n=2) – change of "more time" 9% (n=1) – any change 9% (n=1) – "a little more time" for question 4 (early warning symptoms) 9% (n=1) – "a little more time" or "more time"

Participants were asked how much change they would consider meaningful on the PGI-S, PGI-C, and TTP questions. More than half of participants would want a rating of "I did not have" or "mild" on the PGI-S items. On the PGI-C items, approximately half of respondents needed to see a change of "a little better" and half needed to see a change of "much better". On the time in sunlight questions, most respondents would consider a meaningful change of "more time" or "much more time" in sunlight. Most participants found the questions easy to complete (78–100%). Table 5 contains a sample of these items and summarizes the responses.

Discussion

The goal of this qualitative research study was to better understand the symptoms and daily activity impacts experienced by individuals with EPP and to use this information to confirm the content validity, relevance, and clarity of newly developed PRO measures of severity and change in EPP. A total of 23 combined concept elicitation and cognitive debriefing interviews were conducted: 17 with adults with EPP and 6 with adolescents with EPP.

The results of these interviews revealed that individuals with EPP experience numerous symptoms with significant variability and range. The most common symptoms reported were burning, pain, swelling, tingling, itching, sensitivity to touch, warmth/heat sensation, blisters, redness/discoloration, and sensitivity to hot/cold, which is consistent with previous studies.[1,3] Though burning and pain were reported as distinct symptoms by some participants, consistent with previous studies and case reports,[5,28,29] others reported "burning pain". It is likely patients interpret these concepts on a continuum when describing their symptoms. Most participants report that pain from a full reaction is preceded by tingling/itching/burning sensations of varying severity. Eighty percent of participants who were asked reported that pain was the worst symptom of a full reaction.

Participants also reported being negatively impacted in terms of their ability to do daily activities, social functioning, and emotional functioning, again consistent with results from previous studies.[4,10,19] However, more specific details were obtained in this current study, as well as the view of several adolescents which is novel. Many participants also reported impacts in terms of their ability to work for pay and be productive at their job. Understanding these impacts is critical to ensuring appropriate existing scales are used in this patient population, and that newly created PRO measures encompass domains that are important to patients and not included in existing scales.

Participants were asked to review and complete the newly developed PRO measures assessing full reactions and ability to do activities (EPP Impact Questionnaire). Finally, EPP severity and change in severity of early warning symptoms, full reactions, and EPP were developed as single-item measures (PGI-S and PGI-C). All measures were found to be comprehensive, clear, and relevant.

Our comprehensive concept elicitation resulted in a PRO measure that captures impacts that are important to patients. While some items of the EPIQ appear similar to the previously developed "EPP-QoL", it is important to note that the phrasing of the EPIQ items were developed with direct patient input and carefully debriefed to be clear, which was not the case for the development of the "EPP-QoL". As well, due to issues with the "EPP-QoL" well-being domain, only a "EPP Symptom" domain is recommended for use.[25] Therefore, the EPIQ items that capture effects on daily activities are particularly relevant. Finally, the EPIQ contains several concepts that are not included in the "EPP-QoL" such as changes in overall EPP severity and comparisons to individuals without EPP.

There were numerous strengths to this study; it included a fairly heterogeneous sample in terms of demographic characteristics such as gender, education, marital status, and household income. The demographics were also representative of the EPP population and consistent with characteristics reported in a larger observational study of individuals with EPP in the US.[1] Saturation of concepts was reached by the 11th interview for the total sample, by the 10th interview for the adult population, and by the 5th interview for the adolescent population (Table 3). The sample was also geographically diverse.

This study contained a number of limitations. The sample included both adults and adolescents; however ideally a larger sample of adolescents would have enrolled (although saturation was reached with the sample of 6 adolescents). In addition, the majority of the sample were White, non-Hispanic, and all from North America. Different results may have been obtained with a more diverse sample. It is possible that results would differ if more participants were on an effective treatment. However, our goal was to evaluate pre-treatment symptoms. The impact of other complications of EPP such as anxiety, depression, or liver disease are not specifically assessed in the EPIQ. As well, due to the number and length of the questionnaires, not all items could be cognitively debriefed. Finally, due to the length of the interview, not all interview questions could be asked of all participants.

Conclusion

EPIQ is a novel PRO measure assessing overall EPP severity and has the potential to be a well-defined and reliable endpoint measure of therapeutic response in future clinical trials. In addition, the EPIQ directly assesses patients' prodromal and full phototoxic reaction symptoms which can be used in conjunction with a PRO measure of time-to-prodrome to capture more

comprehensive information. The study demonstrates that EPIQ addresses the gaps in existing EPP measures as a result of having the patient voice drive its development ensuring the creation of a robust and comprehensive measure. Future studies may wish to assess its measurement properties, specifically internal consistency reliability, test-retest reliability, construct validity, known groups validity, and responsiveness. Important within-patient change should also be evaluated using anchor-based approaches.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by an IRB and all participants consented.

Consent for Publication

All participants consented to publication with consent to participate in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. SDM, HHC, LB, and HN were primarily responsible for the design, content, and interpretation of the study.

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GM and WS are employed by and have a financial interest in Disc Medicine. SDM is an employee of Health Outcomes Solutions (HOS), and HHC is a consultant to HOS, which received funding from Disc Medicine for the conduct of this study, and LB is a consultant for Disc Medicine. In addition to funding from Disc Medicine related to this work, LB has past and ongoing research support and contracts from various non-profit organizations and for-profit companies that are unrelated to this work. HN consults for Alnylam Pharmaceuticals, Recordati Rare Diseases, and Mitsubishi Tanabe. The authors report no other conflicts of interest in this work.

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