

**American Porphyria Foundation**

**The Voice of the Patient**

**Patient-Focused Drug Development Meeting**

**Acute Porphyrias**

**Public Meeting: March 1, 2017**

**Report Date: April 1, 2017**

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## **Meeting Agenda**

- 8:50 am Welcome, Introductions and Meeting Goals  
Desiree Lyon Howe, Executive Director, American Porphyria Foundation  
Houston, Texas
- 8:55 am The Role of Patients in Drug Development  
Richard Moscicki, M.D., Deputy Director for Science Operations, Food and Drug Administration  
Silver Spring, Maryland
- 9:05 am Overview of Acute Hepatic Porphyrias  
Herbert Bonkovsky, M.D., Wake Forest Baptist Medical Center  
Winston-Salem, North Carolina
- 9:20 am Current Treatment and Unmet Medical Needs  
Karl Anderson, M.D., University of Texas Medical Branch  
Galveston, Texas
- 9:35 am Therapeutics in Development  
Robert Desnick, M.D., Ph.D., Icahn School of Medicine at Mt. Sinai  
New York, New York
- 9:50 am Patient Panel: Clinical Manifestations, Effects on Daily Life, Quality of Life, and Family Impact
- 10:25 am Facilitated Discussion: Patients, Caregivers, Family Members, and Webcast
- 11:00 am Break
- 11:15 am Patient Panel: Research Participation, Clinical Experience, Impact on Employment, Finances and Treatment
- 11:45 am Facilitated Discussion: Patients, Caregivers, Family Members, and Webcast
- 12:15 pm Questions from Attendees
- 12:40 pm Summation  
John Phillips, Ph.D., University of Utah  
Salt Lake City, Utah

## **Introduction**

On March 1, 2017, the American Porphyria Foundation (APF) hosted a Patient-Focused Drug Development (PFDD) public meeting on the Acute Hepatic Porphyrias. These meetings are a part of the FDA initiative under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. The APF conducted this meeting to enable the FDA to hear an overview of the acute porphyrias, the current and novel therapeutics from esteemed experts in the field and to hear perspectives from people living with acute porphyria. The meeting began with a presentation on the impact of the Patient Voice in Drug Development.

The meeting was webcast and recorded live and can be viewed in its entirety on the APF website home page: [www.porphyrifoundation.org](http://www.porphyrifoundation.org).

More information on the PFDD initiative can be found at:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

## **Welcome**

Desiree Lyon Howe, Executive Director of the APF, welcomed:

- 100** APF attendees, including the 40 patients and caregivers,
- 10** FDA representatives, including Ann Farrell, M.D., Director, Division of Hematology Products, Richard Moscicki, M.D., Deputy Director for Science Operations, Center for Drug Evaluation and Research, and Edvardas Kaminskas, M.D., Deputy Director, Division of Hematology Products,
- 6** Porphyria Consortium Experts, Karl Anderson, M.D., University of Texas Medical Branch at Galveston, Montgomery Bissell, M.D., University of California, San Francisco, Joseph Bloomer, M.D., University of Alabama at Birmingham, Herbert Bonkovsky, M.D., Wake Forest University School of Medicine, Robert Desnick, M.D., Ph.D., Icahn School of Medicine at Mt. Sinai, and John Phillips, Ph.D., University of Utah,
- 11** Pharmaceutical Representatives and
- 80** Webcast attendees.

Desiree then introduced Richard Moscicki, M.D., FDA Deputy Director for Science Operations, Center for Drug Evaluation and Research.

## **The Role of Patients in Drug Development**

Richard Moscicki, MD, Deputy Director for Science Operations, Center for Drug Evaluation and Research

Dr. Moscicki, who has been widely published on the importance of the Patient Voice in the Drug Development process, made a presentation on the present efforts of the FDA to include patient experiences in meeting like the PFDD meetings to improve their understanding of particular diseases. He elaborated that the FDA had held 24 such meetings but the external meetings, like the APF PFDD meeting, allowed the FDA to participate in more face to face meetings. His view was that hearing patients' testimonies allowed the FDA to better comprehend and appreciate the burden of disease, the current treatments and the risks tolerance.

## **Overview of Acute Hepatic Porphyrias**

Herbert Bonkovsky, M.D. Wake Forest Baptist Medical Center

In presenting an overview of the acute porphyrias, Dr. Bonkovsky first discussed the porphyrias in general as a group of at least eight disorders that differ considerably from each other. A common feature in all porphyrias is the accumulation in the body of porphyrins or porphyrin precursors. Although these are normal body chemicals, they normally do not accumulate. Precisely which of these chemicals builds up depends on the type of porphyria. The symptoms and treatment vary significantly from one type of porphyria to the next. Porphyria

symptoms arise mostly from effects on either the nervous system or the skin. Effects on the nervous system occur in the acute porphyrias, Acute Intermittent Porphyria (AIP), Hereditary Coproporphyrinuria (HCP), Variegate Porphyria (VP) and ALAD Deficiency porphyria (ADP). These symptoms include rapid heartbeat, excessive recurrent abdominal pain, hyponatremia, muscle weakness, and dark or reddish urine. Skin manifestations can include burning, blistering and scarring of sun-exposed areas. Proper diagnosis is often delayed because the symptoms are nonspecific. The porphyrias are rare, genetic diseases. The acute porphyrias are estimated at 1 in 20,000 with only 6 cases of ALAD-deficiency porphyria (ADP).

Dr. Bonkovsky noted growing evidence that the key feature of acute porphyrias is the induction of ALAS1. He commented on the “subacute” or chronic symptoms that many patients experience, particularly women with recurrent attacks. In women, attacks were predominantly precipitated by ovulation and the luteal phase of menses. Most patients experienced attacks associated with specific unsafe medications, glucose restrictive diets, and particular hormones. Dr. Bonkovsky also presented the data for the EXPLORE Natural History Study for Acute Hepatic Porphyrias. The data noted that the cardinal feature was severe neuropathic pain in 100% of the attacks. Other symptoms were nausea and vomiting, weakness to paralysis and fatigue. These patients reported a diminished quality of life and significant utilization of medical professionals and frequent hospitalizations. Most attacks required hospitalization. Dr. Bonkovsky suggested that an acute porphyria diagnosis should be considered in all adults with unexplained symptoms (especially women 18-45 years old) with the aforementioned symptoms and dark or reddish urine.

### **Current Treatment and Unmet Medical Needs**

Karl Anderson, M.D., University of Texas Medical Branch

Dr. Anderson discussed the major current treatment, hematin therapy approved as Panhematin, which was the first Orphan Drug in the United States and Normosang worldwide. Although hematin is an effective treatment for porphyria attacks, some patients cannot tolerate Panhematin. He noted, too, the pharmaceutical limitations of hematin treatment and that currently approved treatments need additional research and product optimization. Normosang and Panhematin are “equally effective.”

Because the approved indications of hematin therapy are narrow, randomized clinical trials are lacking. Dr. Anderson is conducting trials now to help patients whose insurance companies are not paying for their treatment and to assist physicians in understanding its indication. Hematin will be needed even if new drugs are approved to treat acute porphyrias.

Dr. Anderson discussed how degradation leads to side effects with hematin and the off label use of albumin. Priorities should be for new treatments for acute porphyrias, increased evidence for hematin, better understanding of the natural history and better supportive treatments for the acute porphyrias, (especially for pain control due to the excessive pain).

### **Therapeutics in Development**

Robert Desnick, M.D., Ph.D., Icahn School of Medicine at Mt. Sinai

Dr. Desnick discussed Panhematin, liver transplant, gene therapy, and RNAi treatment. He provided an update on Panhematin, including the new dosage (350mg per vial), which will be marketed at the same price as the present vial. In July 2017, improvements will be launched to the Panhematin Patient Assistance Program, including co-pay assistance.

He described two cases of liver transplantation: one woman in the UK who has been attack free for 12 years since her liver transplant. He also discussed a woman in the US with severe attacks for 11 years who has been symptom free since her transplant in 2015.

He also discussed the animal and human gene therapy, which though proven “safe” has had no biochemical improvements in ALA/PBG, the indicators of an ongoing attack.

RNAi therapy, “gene silencing approach” to knockdown ALAS1 and then decrease ALA/PBG was also presented. Dr. Desnick noted that the data thus far is very encouraging. Since a virus is not needed, only a small sugar cube can provide the means to perform a subcutaneous injection, which allows the potential for home use. He also noted the natural biologic process, which was the basis of Nobel Prize research.

### **Patient Voice Meeting Overview**

This meeting hosted by the APF provided the FDA representatives with the opportunity to hear face to face from acute porphyria patients, caretakers, and advocates about their perspectives and experiences. The discussion focused on two major features (1) clinical experience and symptoms that are most impactful and (2) patients’ perspectives on current treatment and treatment needs. This was accomplished with two panels followed by a facilitated discussion inviting comments from other attendees both in person and via the webcast.

Approximately 40 patients, who suffered with acute porphyria, attended the meeting in-person and over 80 patients, who participated via the live webcast, provided personal input. According to registration data, in-person and web participants represented a range of patients, with a slightly higher proportion of women, adults aged 18-70+, patients living with the disease for more than 10 years and others only living with the disease less than 1 year. Although participants may not fully represent all of the population living with acute porphyria, the APF believes that the input received reflects a range of experiences with symptoms and treatments of the condition.

To supplement the input gathered at the meeting, patients and others have been encouraged to submit comments on social media and to the APF. Approximately 90 comments were submitted thus far, only 30 days after the meeting. Most comments centered on these topics: Pain, misdiagnosis, need for treatment to prevent attacks and desire to participate in research.

The entire meeting webcast can be viewed on the home page of the APF at: [www.porphyrifoundation.org](http://www.porphyrifoundation.org)  
Or at: <https://www.youtube.com/watch?v=urHxVYVAals>.

### **Report Overview and Key Themes**

This report summarizes the input provided by patients and patient representatives at the meeting and throughout the webcast. To the extent possible, the terms used in this report to describe specific symptoms, impacts, and treatment experiences reflect the words used by the personal testimonies given by the patient attendees. The report is not meant to be representative in any way of the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

Key themes emerged during the Patient Testimonies:

Patients struggled with porphyria attacks, which caused severe, debilitating symptoms, extreme neuropathic pain, nausea, weakness to paralysis, confusion, hyponatremia and fatigue. Over time, these symptoms became chronic in most of the patients. Those with photosensitive acute porphyrias experience burning and blistering of the skin. Most of the patients were limited in obtaining adequate pain relief for their intractable pain and have been considered drug seekers pre and post diagnosis.

Patients experienced difficulty in achieving prevention of attacks and the ensuing symptoms, including intractable pain. Participants described using a complex regimen of both drug and non-drug treatments when pursuing symptom control with a vast range of variability in effectiveness. They shared the significant burden of the two

therapy regimens, the difficulty of weighing benefits and adverse effects when making treatment decisions, and the challenges they faced in obtaining access to prescription drug products.

Patients and families shared the devastating toll porphyria and the neuropathic pain takes on their lives. Many participants described loss or significant changes to their careers, limited social interactions, decreased quality time with family and feelings of hopelessness due to their disease.

Patients emphasized the need for increased awareness and research for new, improved treatments.

The patient input generated through this Patient-Focused Drug Development meeting and public docket strengthens FDA's understanding of the burden of acute porphyrias and treatments currently used to manage its symptoms. FDA staff will consider carefully this input as it fulfills its role in the drug development process; including advising sponsors on their drug development programs and assessing benefit-risk for products under review for marketing approval. This report may be useful to drug developers as they explore potential areas of unmet need for porphyria attacks and porphyria pain. It may point to the potential need for development and qualification of new outcome measures in clinical trials.

### **Patient Panel 1**

Patient Panel 1 addressed the Clinical Manifestations, Need for Assistance, Effects on Daily Life, and Quality of Life Issues with the acute porphyrias.

#### **Lisa: AIP**

Lisa, a 39 year old physician who lost her career, related that attacks were so painful that without pain medication attacks were not compatible with life. This was a recurring statement. She also noted that if there was a 50% chance that she would be well or a 50% chance to die, she would take the risk. Her attacks are so frequent that they are now overlapping. She expressed her concern over her children seeing her life on the sofa or bed and the emotional agony of missing all of their life events.

#### **Heather: AIP**

Heather was diagnosed at 16 and underwent weekly Panhematin infusions for 12 years yet continued to have daily abdominal pain, nausea, fatigue, weakness, burning sensation on her skin and continued attacks. After considering suicide, she heard of liver transplant and chose to take the risk in 2015. Despite the complications (internal bleeding) of such a drastic surgery, she is pleased with her progress and is now, at age 31, attack free.

#### **Terri: AIP**

Terri is a 60 year old woman who was diagnosed at 22 following surgery and administration of unsafe medications. Her subsequent life included the next 5 years in the hospital with the exception of 90 days, then institutionalized in a nursing home at age 27 until 31. Porphyria ended her career and social life. Isolation continues to plague her life as she has since been unable to travel, marry, and bear children because of consistent hospitalizations. She is unable to tolerate Panhematin and has no treatment. She describes her pain as similar to "a belly full of broken glass on fire." She has participated in seven clinical trials and is so desperate for treatment that she is willing to join additional research projects.

#### **Michael: AIP**

Despite an extensive family history, Michael was not diagnosed for eight years. Once finally diagnosed, Michael's doctors refused to prescribe Panhematin treatment. He also was forced to drive 200 miles round-trip for pain management. He said he was "jealous of people with cancer because they have an end – get better or die. Porphyria patients don't get that... they linger in hell." Now he has weekly Panhematin infusions that stop attacks but does not prevent them. He also has had courses of glucose which help but do not stop attacks. Although Panhematin saved his life and stops the attacks, Michael feels we need a prevention drug. He stated that if the new drug does not work, he will be applying for a liver transplant.

**Colin: AIP**

Colin received 80 Panhematin infusions last year and continues to have debilitating attacks that include horrendous pain and encephalopathy. He lives a rigid schedule of physician appointments, hematin infusions, illness for three days and the cycle repeats. His anxiety over having only one treatment is major, particularly if his Panhematin “lifeline” is no longer accessible. He said patients need a safety net, not just one treatment that treats but doesn’t prevent attacks.

**Facilitated Discussion 1**

Following the panel presentations was a facilitated discussion from patients, family members, caretakers and webcast attendees. Desiree Lyon Howe served as the facilitator. The panelists’ testimonies provided a vivid description of what it is like to live with acute porphyria. They described their challenges with diagnosis, their experiences with treatment and achieving pain control, as well as the day to day impact of living with their disease. Although the panelists described the significant physical and social impacts they have experienced, the large-group facilitated discussion that followed the panel discussion provided more in-depth experiences, particularly on the significance and impact of the pain and paralysis, the major symptoms. The additional symptoms discussed were hallucinations, further descriptions of the dreadful pain, overpowering seizures with few safe treatments and the impact of frequent hospitalizations, losing internal organs from misdiagnosis, the problem of misdiagnosis for years and accusations of being a “drug seeker.”

**Ariel: AIP**

Ariel is a 30 year old attorney, who was misdiagnosed repeatedly over a number of years. Misdiagnosis is a major problem with acute porphyria patients. She has since suffered many severe attacks that include the devastating pain noted by the panel, as well as hallucinations, monthly hospitalizations and extreme weight loss. Desperate to find a means to halt the attacks, Ariel has weekly Panhematin infusions, and has volunteered for every clinical trial, including the gene therapy in Spain. Because of her many hospitalizations and illnesses, her hours as an attorney have been greatly reduced as has her earning power. She feels that she is “Not pulling her weight as a human being.”

**Rose: AIP**

Rose has been hospitalized nine times in the last twelve months for an average duration of seven days each admission. She receives weekly infusions of Panhematin, which saved her life but did not restore quality of life. She described her treatment side effects as “infusion hangover.” Between attacks and treatment “hangovers,” 50% of her life is spent extremely ill. Embarrassed when physicians and nurses questioned her condition being real or in “in her head,” or that her pain medications are necessary, she often does not tell them how sick she truly is. Like many patients, she often downplays her illness so that the medical team will not think or write in her record that she is a hypochondriac or drug seeker. This left her without appropriate pain medication and treatment. Her life now is not sustainable and is prepared to take risks on new treatments.

**Jazmine: AIP**

Jazmine was diagnosed three years ago after a lengthy time of misdiagnosis. She was extremely dehydrated and in renal failure at Emory. She had her gallbladder removed without cause, was considered a drug seeker, and wrongly confined to a psychiatric ward. Desperate for treatment, she drives 1 hour to get monthly Panhematin treatment and has become a volunteer for several research projects.

**Kim: HCP**

Kim’s concerns are that medications taken for her other medical conditions (PMS, endometriosis, bladder condition) can cause attacks. She was misdiagnosed for years and is worried that there is no cure or “long term solution.”

**Nichol: AIP**

Nichol's symptoms began four years ago with pregnancy. She lay on a floor in and out of consciousness for six days before she was taken for emergency treatment. After being prescribed an unsafe drug to treat an ovarian cyst, she had a massive hallucination and was sent home w/out treatment. Hallucinations with porphyria are terrifying and should be discussed more. She wakes up every day thinking suicide is the only cure.

**Candace: HCP**

Candace did not receive a diagnosis for 10 years. She suffered paralysis, horrifying pain, seizures and was hospitalized for one year. Despite her inability to walk, physicians thought her paralysis and other symptoms were false until her diagnosis. This was a demeaning experience.

**Evelyn: AIP**

Evelyn has experienced 22 years of brutally intense pain. She lost her position at Homeland Security because of her frequent hospitalizations. She is now on food stamps and Medicaid and lives with her spouse and their four children in her parent's home. She was in the Emergency Room 70 times last year with an average stay of six hours. Evelyn cannot take Panhematin because of a previous pulmonary embolism. Thus, she has no treatment other than daily infusions of D10 which she gives herself. Their family life is difficult. Her husband has trained as an EMT in order to care for her full time.

**Tracy: AIP**

Tracy celebrated the 20th anniversary of her diagnosis. She has undergone extreme paralysis, strokes, and seizures; one of which left her in a coma for six months. Panhematin saved her life, but she needs a treatment to prevent attacks.

**Lina: AIP**

Lina is a college student who must maintain Panhematin treatments to treat her attacks. She is extremely careful of simple, unsafe medications which caused a critical attack.

**Patient Panel 2**

Patient Panel 2 featured Perspectives on Clinical Experience, including Research, Available Therapies and Novel Therapies, Employment, Financial and Daily Life Impact.

**Sharon: VP**

Sharon asked the audience to imagine securing a graduate degree, purchasing her dream home, and having a dream position in her chosen career as Chief Human Resources Officer for the largest oncology group in the USA. Then life changed in 2014 when she woke up with severe pain and unrelenting nausea. She also developed cerebral vasculitis, had three mediport surgeries and has been subsequently hospitalized for 43 days. Also upsetting to her is that she has gained over 50 pounds due to glucose infusions and a sedentary life. Sharon's health deteriorated to such a degree that she is no longer able to be employed and cannot participate in family and social life. She lives in fear her port will clog or that she will no longer be able to access the Panhematin treatment that is keeping her alive. She ended her presentation with her thoughts, "It never occurred to me one day that I'd wake up and never get better."

**Mary: AIP**

Mary's work as a toy company executive took her around the world until the "Sleeping dragon woke up." Her doctor diagnosed her quickly after watching *The Madness of King George*. Unfortunately, she suffered 200 attacks and had to have six ports replaced for Panhematin infusions. The port infections caused pseudomonas sepsis and endocarditis. When Panhematin was not available for a week, she had her worst attack. She had respiratory arrest and paralysis that left her hand partially paralyzed. Her quality of life continues to decline. Panhematin is her treatment but it does not prevent attacks so she is desperate for a treatment. Her health pre-

vented her from keeping her executive position which forced her to lose her home and live with her parents for 18 years. Over the last year, she has had twelve attacks and seven hospitalizations.

### **Amy and Craig: AIP and Caregiver/Husband**

Amy's consistent illness makes any normal activities like a career or daily and social activities of living unrealistic. She noted that she has received countless medical bills in excess of several hundred dollars and is frightened about how to pay them. Hospitals often code the illness incorrectly, so hospitals bill in ways insurance companies will not reimburse. She told the participants that they must be constantly vigilant to make sure they do not have insurmountable medical bills, at times when they are least capable or willing to think of anything but trying to get better. Amy had to leave her job in the financial industry. She is desperate for treatment because she had had a number of life threatening attacks. In search of a better treatment, Amy has joined all of the present research studies.

Craig, Amy's husband and caretaker, had difficulty in interpreting and understanding Amy, especially when she was experiencing "mental fog." He encouraged other caretakers, "It takes time and effort to develop how to communicate. It is constant work. There is a great degree of diagnostic hubris by people in the healthcare industry. They are dismissive, i.e. 'How do you, as a lay person, understand porphyria?'" He continued, "Patients are smart!" Craig is protective of Amy when she is ill and assures that she has the best medical care. He feels that new therapies are essential. Craig extrapolated figures related to the enormous economic loss to the country of porphyria people unable to participate in the workforce.

### **Cheryl: AIP**

During her first life threatening attack, Cheryl suffered a seizure, was ventilated, and paralyzed, and remained in a wheelchair for over a year. She remained undiagnosed until 2015. She is devastated that her two children might have the disease and suffer the stabbing, aching pain in her back that she suffers. Her father was later identified as being a carrier of porphyria, and he died soon after his diagnosis.

### **Louise: AIP**

Louise grew up thinking debilitating pain was normal. During her first attack, her doctors discussed removing organs. After a long 28 year journey, she was finally diagnosed. She was the owner of several successful businesses, had two homes and was the mother of four children. However, because of AIP, she lost her business, her homes and her normal life and was forced to live on disability. Her medical records are replete with "drug seeker." When attacks came weekly, her doctor arranged for home hospice and Panhematin. She continues to live with constant pain, has had ten ports and 17 PICC lines. She now has no more access to treatment so she lives in fear. She is desperate for another therapy.

### **Tara: AIP**

Although she had symptoms, such as severe abdominal pain, since age eleven and a family history of the disease, she was not diagnosed for a decade. The family did not share that porphyria was in the family because of the social stigma associated with genetic disease. Tara has had over 100 hospitalizations with even more Panhematin infusions. She has had three ports and has home infusions with home healthcare. She says, "Porphyria has taken everything away from me. I wanted to be a forensic scientist and had to give up my career. My ex-husband took my children away because he claimed I was an unsuitable mother because I was ill all the time." She has not seen her children in five years and feels overpowered for the legal battle ahead. She states that more treatments are needed.

### **Jackie: AIP**

Jackie and all three of her daughters have AIP and stage three kidney failure. Her brother died from the disease. When she is ill with an attack, she says, "I cannot work, and need assistance with everything." Many doctors told her she has nothing wrong and her ailment was in her head. She does not tolerate Panhematin and is fearful

that there is no other therapy. At the American Porphyria Foundation she has finally found people who understand her.

**La Toya: AIP**

La Toya was diagnosed after a lengthy time of misdiagnosis. She suffered with severe, stabbing pain, a host of other signs and symptoms, and neurologic symptoms, namely weakness and debilitating pain. Finding it hard to heal and recuperate, it takes longer and longer to recover. She cannot tolerate Panhematin and almost lost her life when she received the drug the first time. She noted she has just lost her new job and her spouse. The disease makes it hard to care for the family and puts pressure on the marriage. She has no therapy and is fearful that there will not be another treatment.

**Danielle: AIP**

Danielle watched her mother die from AIP in her early 30s. Danielle was part of the DNA studies and was diagnosed before becoming symptomatic. When she had her first attack, she could not believe how severe the pain could be. She remained in the hospital for a week, incurred terrible hospital bills, and lost her job over months of incapacity. In turn, she also lost her medical coverage. She made the decision to not have children so as not to put her children through the journey that killed her mom and ruined her life.

**Lakeshia: AIP**

Lakeshia is 29 years old and has had fierce, chronic nausea and chronic abdominal pain since she was a teenager. She also suffered extreme memory loss during attacks. She searched for a diagnosis for ten years and her weight decreased from 126 pounds to 80 pounds. Hoping to find a new drug to stop her attacks, she has volunteered for all acute porphyria studies.

**Diana: AIP**

Diana's first attack was three years ago at age 29. Because of a family history of acute porphyria, her diagnosis was quick after she suffered what she describes as the "worst pain of my life." Her mother died of porphyria-related renal failure. Diana's attacks were weekly, so she receives weekly Panhematin infusions. She is a former school teacher and had to give up teaching due to her frequent attacks. She participates in several clinical studies and wants to help develop a therapy that can treat this disease.

**Facilitated Discussion 2**

After hearing the second panel, other patients, family members, caretakers and webcast participants built on their experiences. Desiree Lyon Howe again served as the facilitator. The panelists' testimonies added graphic description of the impact on their financial lives, employment, family lives and health. They described their challenges with diagnosis, their experiences with treatment and achieving pain control, as well as the day to day impact of living with their disease. Although the panelists described the significant physical and social impacts they have experienced, the large-group facilitated discussion that followed the panel discussion, provided more in depth experiences, particularly on the significance and impact of the pain and paralysis, the most significant symptoms. The additional symptoms discussed were hallucinations and seizures. The additional disease impacts discussed were frequent hospitalizations, losing internal organs from misdiagnosis, loss of employment, exorbitant medical bills, and the problem of misdiagnosis for years and accusations of being a "drug seeker."

Many of the public comments focused on problems in the Emergency Room and in the hospital.. In the ER, the patients were often not believed that they suffered from porphyria even when they submitted their diagnosis and official records. This caused delayed treatment of the attack and delayed pain management. Both delays prompted the attack to worsen and in some cases create a life threatening attack.

In the hospital setting, many patients used the public comments to address their repeated problems with hospitalists. Since acute porphyria is rare, it is unlikely that they have ever seen a case of acute porphyria. Yet, most often the hospitalist refuses to heed the primary care doctor's orders regarding pain medication, glucose, and Panhematin. Over thirty patients commented that they had been taken off of their pain medication and given a very small dose of either the same medication or a different medication. On four occasions, the medication was on the unsafe list. It is very difficult for physicians with little knowledge of the porphyrias to understand the need for such copious amounts of pain medication. Therefore, they take action to change the patient's dose without consulting with the primary care physician. This not only increases the suffering but places the patients in undue stress, which, in turn, intensifies the attack.

Additionally, two patients believed that by delaying Panhematin treatment, their hospitalist caused paralysis, coma and months of hospitalization and physical therapy.

### **Common Themes from the Patient Panels and Discussions include:**

- Patients described porphyria pain as “hell on earth and incompatible with life,” thus they were desperate for a new treatment.
- Physicians misdiagnose acute porphyria often and are reluctant to diagnose even with a family history.
- Physicians are reluctant to believe patients are truly ill or are not willing to care for a rare disease.
- Most patients had been deemed hypochondriacs and “drug seekers,” and had this demeaning tag posted in their medical records.
- Patients, as a rule, endured repeated misdiagnosis. A very few were fortunate to be diagnosed quickly.
- Only opioids can even put a dent in the pain and for some only after days of use.
- Many patients received Panhematin, glucose infusions and GnRh treatment.
- There is “Nothing intermittent about acute intermittent porphyria!”
- Patients spend an enormous amount of time hospitalized or ill.
- The emotional and mental pain of not being able to be a productive person is overwhelming.
- Many experienced extremely severe symptoms such as paralysis, seizures, comas, respiratory failure, etc.
- Many lost spouses and some even lost custody of their own children.
- Most have participated or are willing to participate in trials.

### **Patient Perspectives on most significant symptoms**

One patient submitted the following from the public comments that most effectively illustrates the major symptom of acute porphyria, PAIN, “My nurse came into the room and tried to compare her back ache with my porphyria pain. The problem with that is there is NO PAIN LIKE PORPHYRIA PAIN. THERE CAN BE NO COMPARISON. This pain is not of this world.”

During the panel discussion and facilitated discussions, patients stated that the neuropathic pain and paralysis they experienced were their most significant outcomes of living with acute porphyria. Participants expressed variation in the frequency, intensity, and type of pain they experienced. The “head to toe” paralysis and partial paralysis that occurred from an attack was another outcome that was terrifying to patients who had suffered paralysis once and knew it could return. Some patients were still unable to walk or use their hands. .

In-person and web participants provided in-depth perspectives on pain experienced primarily in the abdomen. Most often the participants described their pain as burning and the intensity in terms like, incompatible with life, suicidal pain, brutal, devastating, unbelievable and incomprehensible pain and indescribable. Specific, detailed, vivid descriptions of abdominal pain included,

- a thousand flaming swords,
- volcanic lava churning,
- a searing poker,
- a blow torch,
- burning steel spikes,
- tased by a field of enemies,
- electrical shocks,
- lightning bolts,
- broken glass churning on fire and
- burning from the inside out.

One participant submitted the following picture he created to describe his pain because he felt words could not convey the intensity of the pain.



During the comments opportunity, at least 90% of the participants said they were currently in pain during the meeting. It was brought up repeatedly that patients often struggled to gain appropriate pain management and even still they felt accusations of disbelief that their pain was as severe as they were describing to the medical team.

Paralysis was also a serious manifestation of porphyria. Participants described their paralysis as an outcome of a critical, life threatening attack. The paralysis lasted from six months to a year. Several people never recovered from the paralysis and were left with partial paralysis in their hands, arms and/or legs.

### **Impact of Porphyria on Daily Life**

Both patient attendees and web participants described in vivid detail the impact that acute porphyria has on their daily life in terms of the physical illness and the emotional burden of depression, suicidal thoughts, anger, sadness, and other emotional distress. These impacts include:

#### **Impact on daily activities**

Participants expressed how acute has affected their ability to perform even basic activities of normal life from caring for themselves to caring for children and their home. They were hospitalized frequently and unable to participate in daily chores. They feared they would become housebound. One participant noted her daughter had to care for her totally in an attack. Patients were forced to live with their parents for financial and caretaker reasons. One husband gained an EMT degree to directly care for his wife. Most participants expressed their distress at not being a productive person in their homes and communities.

#### **Impact on employment**

Most of the attendees discussed hardships at work and eventual loss of their jobs due to frequent hospitalizations and illness. One patient who had been a physician shared that she had to stop her career after a decade of education because she was ill and hospitalized more time than she was well. Two executives and business owners lost their homes, jobs, and ability to earn an income. A young attorney was forced to decrease her work hours and another had to change careers because the long hours and stress were too much on her body and kept her ill. The men were distressed about not being able to care for their families. One of the attendees was forced to live in a homeless shelter. Most were forced to live on disability. All but three of the participants were unable to engage in gainful employment. Even when procuring a new employment opportunity, they were unable to hold the job because of missing too much work, limitations on time at work, cognitive issues, and fatigue.

### **Impact on finances**

All of the attendee participants were financially impacted. One woman noted her hospital bills are over \$200,000 with each hospitalization. The insurance company will not pay for her Panhematin. One key factor often repeated was the inability to pay for treatment and insurance payments. Financial devastation was the plight of 95% of the attendees. With no way to earn money, most lived below the poverty line, lived with family or were supported by a spouse.

### **Impact on relationships**

Participants addressed how porphyria attacks affected their relationships within their families and among friends. Divorce was a frequent occurrence. The subsequent emotional upheaval was shattering for patients and some even suffered attacks due to the stress of the divorce. Stress of an illness or emotional stress can precipitate attacks. Several patients were concerned that their health put too much strain on the caretakers/spouses. Some families would not accept the diagnosis and others were embarrassed by having a genetic disease and kept the diagnosis a family secret.

Unsettling was the fact that some children were left to care for themselves as the simplest tasks, like cooking, laundry, and homework were often too difficult when the patient was ill. Also upsetting was that children watched their parent lay suffering, barely able to function, could not be a part of their lives and had to watch the family activities from afar instead of being a part of them. Frequent hospitalizations and critical attacks were fearful for children. One woman lost her children because she was hospitalized so often. She has not had the emotional strength to win them back or the finances to hire lawyers to fight her case. This experience has been substantiated and is a heart wrenching story.

Commenters expressed that they experienced loss of family and friend connections due to their disease. It is difficult to maintain friendships while continually having to back out of planned visits, dinners, etc. It is difficult for family and friends to understand acute porphyria and the accompanying neuropathic pain and other severe symptoms, particularly when symptoms are intermittent. It is also hard for them to comprehend why a patient cannot commit to any long-term plans, as the patient never knows when the attack will incapacitate. Social isolation often follows as even old friends drift from the relationship. Participants attributed their lack of social engagement to remaining mainly “house-bound” or “bed-ridden” due to pain. A few commenters noted that pain, nausea, etc., has affected their mood and caused them to become anxious, impatient and intolerant when interacting with friends and family.

### **Impact on self-esteem**

When a physician was unable to find a diagnosis for the patients, most were told that their illness was “in their head,” or they were advised to consult a psychiatrist. Worse yet, the presenters were deemed “drug seekers. Unfortunately, the “drug seeker” tag was posted in their medical record. They said that once the “drug seeker” or “needs a psychiatrist” label was noted in their medical record, they found it difficult to have the label expunged from their record. Patients also revealed that they had been placed in psychiatric wards as a result of misdiagnosis. When it was discovered they were not mentally ill but physically ill with porphyria, they were treated appropriately. However, some had experienced lengthy hospitalizations in mental hospitals until the porphyria was discovered and became stigmatized when they were not mentally ill. Instead they were in the midst of an attack. Attacks can cause mental symptoms from mild anxiety to hallucinations. Being mistakenly placed in a mental institution impacts the patient’s self-esteem, not to mention the trauma of such an experience. Each of these medical mistakes contributed to lowered self-esteem as has the patient’s inability to be gainfully employed and inability to help at home.

### **Impact on fears about the present and the future**

Several participants focused on their concerns about the future, particularly regarding disease progression, finances and longevity. Their fears were not unfounded as most of the patient presenters suffered frequent, se-

vere attacks. Some were fearful that they, too, would become paralyzed and be unable to perform the simplest tasks or would die and leave their children parentless. They feared becoming housebound. A few participants also expressed concern about their ability to adequately manage their pain as their symptoms worsened.

Presenters also were frightened about the present, as well. Those who could not tolerate Panhematin were alarmed that the next attack could be the last and would end in death. Many lived in fear of the symptoms of an attack, particularly the devastating pain. Some of the patients suffered anxiety and panic attacks when they experienced the disease prodrome because they knew and feared the pain, potential paralysis, seizures, etc. would be upon them shortly thereafter.

The majority of patients feared discussions about their pain medication. Since opioids are the primary means for pain treatment, medical professionals new to their cases often changed their medication dosage or took it away completely. One patient had to drive 100 miles each way to receive 10 pills per trip with the promise that each time one pill would be taken away. For a patient in the excruciating pain that acute porphyria patients live in, this is terrifying news. They know that their pain cannot be controlled with minor drugs and that many drugs other than opioids are on the unsafe list or will not halt the intense pain they are experiencing. During an attack, patients are given IV opioids to quell the extreme pain.

Most of the presenters and commenters noted in their presentations and subsequent statements that when they were admitted to the hospital, the hospitalist would change the orders of primary care physicians, especially the pain medication orders. Nurses also would make disparaging comments about “drug seeking.” This occurs more than 90% of the time in Emergency Rooms and hospitals when a new physician takes over the patient’s case.

When the patients must seek a new pain management team, they again are met with disbelief and accusations. These physicians generally have little, if any, knowledge of the acute porphyrias or the level of pain that patient’s experience. However, most doctors immediately lower the pain dosage radically and/or require a stringent, unattainable contract about the patient’s drug use. Although this contract may be tenable when a patient is not in an attack, it is unrealistic during an attack. Having their medication changed or taken away was a fear that was a very real fear that occurs often in the hospital.

### **Patient Perspectives on treatments for Acute Porphyrias**

Most of the presenters received Panhematin. Others received glucose and Lupron therapy. Their perspectives were important as was the show of hands that indicated over 95% of the patients were willing to join a research study.

They expressed gratitude that Panhematin saved their lives and it was effective for stopping attacks. Others could not take Panhematin for a host of reasons. They were also bounded by cost, port problems and access issues. However, 100% of the commenters were adamant that they needed a treatment to prevent attacks from occurring.

Since menses can precipitate attacks in women, some women with menstrual related attacks were treated with GnRh treatment to stop the cycle and, in turn, stop attacks. Although this worked for some, it was not well tolerated and did not stop attacks for most. It did, however, help slow the number of attacks in some of the women who were able to tolerate Lupron. It was only a treatment for women.

Others received glucose. Although glucose can help, it does not stop attacks and does not help much in severe attacks. Some of the commenters had glucose daily or several times a week. One person received D10 infusions daily, which she infused herself. Despite the daily infusions, this patient has been to the Emergency Room 70 times in the past year. In all cases, glucose did not stop attacks.

## **Perspectives on Current Treatments**

In the panel and the large-group facilitated discussion, at least 90% of patients and patient caretakers expressed gratitude that Panhematin saved their lives and was an effective treatment to stop attacks. They were grateful that they had Panhematin but expressed fear of having only one treatment. Others could not take Panhematin for a host of reasons. They were also bounded by the cost of Panhematin, problems with their infusions as ports broke often, doctors unwilling to administer Panhematin and problems with access after many Panhematin infusions were administered. However, 100% of the commenters were adamant that they needed a treatment to prevent attacks from occurring.

Some women were prescribed Lupron to stop the menses and, in turn, stop attacks. Although this worked for some, it was not well tolerated in others and did not stop attacks for most. It was only a treatment for women.

Most received glucose at one time or another. Although glucose can help, it does not stop attacks and does not stop severe attacks. A few commenters had glucose frequently while a few others had glucose during attacks. One patient, who could not take Panhematin, received D10 infusions daily, which she infused herself.

Participants tried a host of pain relief tools, including biofeedback, TENS units, massage, meditation, Gabapentin for nerve pain and over the counter pain medications. None worked well.

## **Perspectives on novel therapeutics and the desire to participate in RESEARCH**

Throughout the meeting, participants provided perspectives on the ideal treatment, which would be a treatment that prevented attacks from occurring. Some of the presenters were involved in trials for a new therapy but did not talk about the study. Most spoke about their repeated attacks, hospitalizations, coma, paralysis, and exceedingly difficult symptoms like, nausea, pain, and hallucinations. Participants also desired an ideal treatment with fewer long-term and short-term side effects. Present treatment side effects can be quite serious, including headaches, vomiting and flu-like feeling.

By a show of hands, over 95% of the patient attendees were willing to participate in a trial to find a treatment to prevent attacks. One of the presenters described her experience in all studies for acute porphyrias, including gene therapy. She said that trials were the only thing that gave her the willingness to live. To her, trials provide the means to move the treatment and cure needle forward and for hope for her and her children along with for other patients and all of their children.

Another presenter explained how difficult it was for patients to participate in research. Getting in the car to go to the airport was hard as she had just been released from the hospital the week previously. When flying to the research center, she needed two relatives to care for her. When the first day of the trial was over, she said she was willing to continue, because if people didn't advocate for themselves, "WHO WOULD!" (As an aside, since the meeting, this patient volunteered for another major research project.)

## **Questions**

Dr. Robert Desnick moderated the Question-Answer Session of the meeting. Questions were gathered from attendees, including the FDA, patients and webcast participants. Dr. Robert Desnick first spoke on the courage patients had to openly share their lives.

### **Question 1: Patient**

How do we make doctors understand, especially with the rarity of the patients?

Desiree answered that, with great effort, the APF has major physician education programs that provide resources. Patients can also help by educating their own doctors and having them sent an educational packet from the APF.

Dr. Desnick also noted it is difficult as there are over 10,000 rare genetic diseases. When there is a treatment for a condition, it will raise awareness and prioritize the education of treatable conditions.

Dr. Karl Anderson commented that it would be helpful to have porphyria be part of the diagnostic workup for abdominal pain. As a hepatologist, we have rare diseases as part of standard differential diagnoses for liver dysfunction, even when there is a low index of suspicion. We need a similar approach to this for abdominal pain.

### **Question 2: FDA**

Dr. Ann Farrell, Director, Division of Hematology Products: How many of the patient attendees have participated in a clinical trial? By a show of hands, 85% of patients had volunteered for a trial and over 95% would volunteer for a trial for a new therapy.

Dr. Farrell: Can anyone speak to their experience in a clinical trial?

Patient: Ariel said she has participated in every trial for which she has been eligible. She even moved her family to Spain for the Gene Therapy clinical trial. Even though the therapy did not work, she felt she had contributed to helping move the needle closer to discovering a new therapy. She felt the same with all research efforts.

Patient: We are willing to travel to participate in clinical trials and do whatever it takes because we must be our own advocates.

Dr. Desnick: The NIH supports the Porphyria Research Consortium of experts. We have 8 sites for porphyria clinical studies. Over 200 patients have participated in these PC studies.

### **Question 3: Patient**

Desiree asks a question from the webcast participants. Why do some people have their diagnosis taken away?

Dr. Karl Anderson noted that there are some patients misdiagnosed as having porphyria, and it is better to know what these patients have when it is not porphyria. His opinion was that it is not good for the patient to continue on with the wrong diagnosis. Also, patients may have chronic pain in the absence of elevated ALA/PBG.

Dr. Desnick: Experts throughout the world use biochemical testing for PBG and/or ALA in the urine, sometimes in the plasma. The gold standard for biochemical tests are urine PBG/ALA analysis. Patients are also often genotyped through DNA testing.

### **Summary**

Dr. John Phillips, of the University of Utah, provided the meeting summary.

Dr. Phillips began his presentation by thanking Desiree Lyon Howe and the APF, patients in attendance, and the FDA. This dialogue between federal regulators, medical experts, patient advocacy groups, and patients helps everyone better understand how to identify clinical questions that need to be addressed in an attempt to develop new therapies.

Dr. Phillips stated that there is clearly an unmet need for education. Therefore, widespread physician education is very important. The APF has many educational resources available for patients, caregivers, doctors, etc.

Throughout his presentation, Dr. Phillips discussed the disease, current and potential treatment options, quality of life, financial burden, and unmet medical needs within the porphyria community. By the show of hands, it was evident that patients are willing to participate in future trials for new therapies. This gives hope that there will be options available to everyone as we move forward toward to research more treatment.

Dr. Phillips related that not only did patients face a tremendous physical burden with the acute porphyrias, they also face a significant financial burden, which often leads to financial ruin. He urged, “We need to understand the cost to society for this group of rare disorders.”

### **Conclusion**

This APF hosted PFDD meeting provided an opportunity for the public and the FDA to hear personal, in-depth patient points of view on the severity of acute porphyria and how this group of diseases impact normal life. They heard how current treatment is effective in stopping attacks, but treatment is greatly needed to prevent attacks.

The APF is very grateful to all of the participants who suffer with the acute porphyrias and who courageously shared their personal experiences.