

Disease Burden and Healthcare Resource Utilization among Patients with Acute Intermittent Porphyria Experiencing Chronic Pain: Analyses from a National Healthcare Database

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Background and Rationale

Acute Hepatic Porphyria (AHP)

- Family of rare, genetic diseases due to a deficiency in one of the enzymes in heme biosynthesis in the liver^{1,2}
 - Acute intermittent porphyria (AIP) is the most common type, with mutation in the hydroxymethylbilane synthase (*HMBSS*) gene^{3,4}
- Patients can experience:
 - Acute neurovisceral attacks which commonly manifest as severe abdominal pain and can be life-threatening^{5,6}
 - Debilitating chronic symptoms (pain, fatigue, nausea, and anxiety)⁵⁻⁷; neuropathic pain is often refractory to treatment⁸
 - Hypertension, chronic kidney disease, and liver disease^{3,5,9-11}
 - Disability, diminished quality of life, and social isolation⁵⁻⁷
- Current literature and clinical practice largely segment AIP disease severity by presence or lack of symptoms and frequency of attacks
- Attacks are treated with intravenous (IV) glucose and/or hemin, while prophylactic treatments include off-label IV hemin, and subcutaneous givosiran, which was recently approved in the USA for the treatment of AHP in adults and in the EU for the treatment of AHP in adults and adolescents aged 12 years or older^{6,12,13}

Objective

- To identify patients with AIP diagnosed in a nationally representative healthcare database to estimate healthcare resource utilization among various patient segments defined by attack rates, chronic symptoms, and comorbidities

Methods

Retrospective Claims Database Study Design

- This retrospective analysis utilized the IBM[®] MarketScan[®] Commercial Claims and Medicare Supplemental Databases to identify patients with at least one claim for AIP (ICD-10 diagnosis code E80.21) between October 1, 2015 and June 30, 2018
- The subset of patients with AIP with continuous enrollment for at least 1 year following their first observed AIP diagnosis (index date) were identified for assessment of baseline characteristics and post-diagnosis (post-index) outcomes, including healthcare resource utilization, medication use (including hemin), symptoms, and the frequency of comorbid diagnoses (Figure 1)
- Patients with AIP were segmented by frequency of attacks, presence of chronic symptoms using medication possession ratios (MPRs) (Figure 2) of analgesics, and the presence of comorbidities (e.g., liver disease, renal disease, and chronic neuropathy)
- Analysis focused on the patient segment specific to chronic pain, defined by the upper quartile MPR (>0.68) of patients with AIP with claims for opioids. Means were reported as per patient per year to account for the variable length follow-up

Figure 1. AIP Patient Characteristics Observation Period

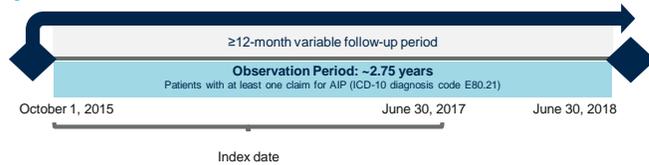
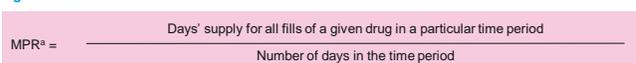


Figure 2. Medication Possession Ratio Calculation



*MPR is used to measure patients' medication adherence, defined as the proportion of a time period where a medication supply is available¹⁴

Results

Patient Demographics and Characteristics (Table 1)

- 225 unique patients with symptomatic AIP were identified with ≥12-month follow-up between October 1, 2015 and June 30, 2018
- From these, two subgroups were identified: 1) patients experiencing chronic pain (upper quartile of opioid use, and 2) those experiencing recurrent attacks (≥3 attacks per year)
 - Subgroups were not mutually exclusive

AIP Attacks and Hemin Use

- Patients with chronic pain experienced a mean of 2.5 attacks per year compared with all patients with AIP (2.2 attacks) and recurrent attack patients (5.2 attacks; Table 1)
- 14 of the 37 (38%) patients with chronic pain were not actively experiencing attacks (Table 1)
- Hemin treatment was given to 19 (8%) patients in the all patients with AIP group, 8 (22%) patients in the chronic pain group, and 10 (28%) patients in the recurrent attack group

Table 1. Patient Demographics

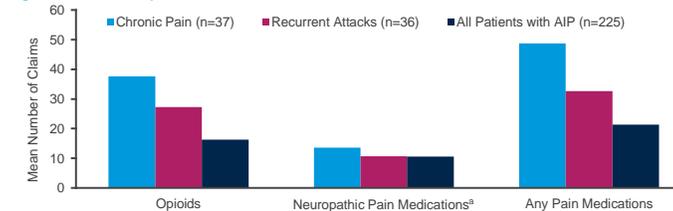
Characteristic	Chronic Pain (n=37/225)	Recurrent Attacks ^a (n=38/225)	All Patients with AIP (n=225)
Age, years (SD)	48.4 (12.4)	39.2 (15.2)	45.6 (16.4)
Female gender, n (%)	29 (78)	25 (69)	157 (70)
Mean observation time, years (SD)	1.93 (0.6)	1.79 (0.6)	1.89 (0.6)
Payer, n (%)			
Commercial Medicare	36 (97)	32 (89)	207 (92)
Medicare	1 (3)	4 (11)	18 (8)
Population density, n (%)			
Urban	37 (100)	31 (86)	196 (87)
Rural	0 (0)	5 (14)	28 (12)
Unknown	0 (0)	0 (0)	1 (0.4)
Mean attacks per year	2.5	5.2	2.2
Patients with 0 attacks, n (%)	14 (38)	0	104 (46)
Patients with ≥3 attacks, n (%)	13 (35)	36 (100)	53 (24)

^aRecurrent attacks are defined as ≥3 attacks per year. Attacks are defined as an outpatient emergency department visit or inpatient admission with a diagnosis of porphyria, abdominal pain, back pain, chest pain, or nausea/vomiting in any position on the claim. For patients who do not have any indication of prophylactic hemin use, use of hemin will also be counted as an attack. Attacks identified within a 7-day period were counted as a single attack

Prescription Medication Use

- A total of 149 patients with AIP (66%) had ≥1 opioid claim; there were 37 in the chronic pain group (100%) and 30 patients in the recurrent attack group (83%) with ≥1 opioid claim
- MPR in the chronic pain group was 0.93 for opioids and 0.97 for any pain medication; in the recurrent attack group MPR was 0.32 for opioids and 0.52 for any pain medication
- A majority of the patients with chronic pain (n=21, 57%) had claims for neuropathic pain medications with an average of 14 claims per year (Figure 3)

Figure 3. Mean Prescription Claims



All-Cause Healthcare Resource Utilization

- A total of 91 (40%) patients were hospitalized, with 22 (60%) of these patients falling into the chronic pain subset and 30 (83%) in the recurrent attack subset
- A majority of the patients with chronic pain visited the emergency room at least once (n=21, 57%)
- An average of 81 pharmacy claims per year were captured in the chronic pain subset compared with 59 claims in patients experiencing recurrent attacks (Table 2)

Table 2. Healthcare Resource Utilization

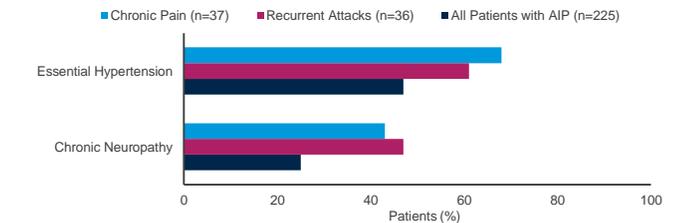
Characteristic	Chronic Pain (n=37/225)	Recurrent Attacks (n=36/225)	All Patients with AIP (n=225)
Hospitalization, mean (SD)	1.0 (1.4)	2.4 (1.8)	0.7 (1.3)
Length of stay, days, mean (SD)	4.4 (2.9)	6.0 (4.4)	5.3 (4.7)
Emergency room visit, median (Q1, Q3)	1.2 (0, 4.2)	8.2 (3.2, 16.2) ^a	0.8 (0, 2.9)
Emergency room visit, mean (SD)	5.0 (9.0)	15.5 (28.8)	3.6 (12.7)
Outpatient office visit, mean (SD)	18.7 (11.7)	19.7 (12.2)	13.6 (10.5)
Pharmacy claims, mean (SD)	80.7 (41.7)	58.7 (33.4)	41.4 (36.1)

^aNote: Median is presented in addition to mean as one outlier patient with 170 emergency room visits was included in analysis

Comorbidities

- Patients with chronic pain and recurrent attacks were most commonly diagnosed with hypertension (68% and 61%, respectively) and chronic neuropathy (43% and 47%, respectively; Figure 4)

Figure 4. Comorbidities



Limitations

- Administrative claims lack detailed clinical information, and it can be challenging to distinguish true diagnoses
- Differences in coding practices may impact results (e.g., hemin use in hospital settings may not be captured)
- Results may not fully represent the range of all patients with AIP due to the analysis sample (e.g., strict requirement for a standard continuous enrollment) and characteristics of the database (e.g., mostly commercially covered lives)
- Indications for neuropathic pain medications cannot be distinguished from pain or depression
- Study captured prescription medication claims only, not over-the-counter medications, potentially underestimating pain medication usage

Conclusions

- The presence of frequent opioid use in this database of patients with AIP suggests that chronic and severe pain is present in the AIP population
- Results from this national representative healthcare claims database demonstrated patients with AIP experiencing chronic pain, as measured by frequent opioid use, have high disease burden and healthcare resource utilization
- Patients in the chronic pain group experienced comorbidities/long-term complications of AIP, despite 38% experiencing no attacks during the observation period

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Abbreviations: AAR, annual attack rate; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; HMBSS, hydroxymethylbilane synthase; ICD-10, 10th revision International Statistical Classification of Diseases and Related Health Problems; IV, intravenous; MPR, medication possession ratio; SD, standard deviation
References: 1. Puy et al. *Am J Hum Genet* 1997;60:1373-83; 2. Balwani & Desnick. *Blood* 2012;120:4496-504; 3. Borokovsky et al. *Am J Med* 2014;127:1233-41; 4. Elder et al. *JIMD* 2013;36:849-57; 5. Gouya et al. *Hepatology* 2019; DOI:10.1002/hep.30936; 6. Pischik & Kauppinen. *Appl Clin Genet* 2015;8:201-14; 7. Simon et al. *Patient* 2018;11:527-37; 8. Wang et al. *Hepatol Commun* 2018;3:193-206; 9. Stewart. *J Clin Pathol* 2012;65:976-80; 10. Pallet et al. *Kidney Int* 2015;88:386-95; 11. Andersson et al. *J Intern Med* 1996;240:195-201; 12. GIVLAARI Highlights of Prescribing Information. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0212194s000lbl.pdf. Accessed August 24, 2020; 13. GIVLAARI EU Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_en.pdf. Accessed September 10, 2020; 14. Andrade et al. *Pharmacoeconomics* Drug Saf 2006;15:565-74