Estimating healthcare resource use associated with the treatment of phenylketonuria in the United States

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Introduction

- Phenylketonuria (PKU) is a rare genetic disorder caused by deficiency of the phenylalanine hydroxylase enzyme, which results in decreased metabolism and elevated levels of the amino acid phenylalanine (Phe) in the blood. These elevated levels of Phe can result in severe intellectual disability, epilepsy, and behavioral problems[1,2]
- Medical nutrition therapy (MNT) – which includes dietary restriction of Phe, supplemented with specialized medical formula with no/low amounts of Phe – has historically been the cornerstone of treatment of PKU,[3,4] with pharmacological therapies becoming available during the last decade[5]
  - The first 2 approved pharmacological therapies for PKU in the US were sapropterin dihydrochloride (indicated for children and adults) and pegvaliase (indicated for adults only)[5–7]
- Medication costs are the largest driver of medical costs for individuals living with PKU.[8] However, the impact of PKU treatment type on healthcare resource utilization (HRU) in the US is currently unknown

Objective

- To estimate the HRU associated with the treatment of PKU in adults and adolescents in the US

Methods

Study design and data source

- This was a retrospective, observational cohort study of adults (aged ≥18 years) and adolescents (aged 12–17 years) with PKU in the US. The study used de-identified claims data from the HealthVerity database (**Figure 1**)
  - HealthVerity is a de-identified dataset comprising medical and pharmacy claims compiled from >75 data providers covering >330 million individuals in the US[9]
  - Patients with PKU were identified based on International Classification of Diseases (ICD)-10 diagnosis codes or receipt of PKU-related treatment
- This analysis covered a timeframe of May 24, 2018, to March 31, 2023 (analysis period; **Figure 1**)
- The index date served as the starting point for an individual's inclusion in the analysis, and was required to fall between May 24, 2018, and March 31, 2022 (index period; **Figure 1**), to allow a minimum of 12 months of follow-up
- Index date was defined as date of first evidence of PKU diagnosis (for individuals with no record of treatment) or first evidence of treatment with pegvaliase, sapropterin dihydrochloride, or MNT
- HRU was evaluated after the index date based on the number of hospitalizations and outpatient visits (by specialty), and the length of inpatient stays

Figure 1. Eligibility criteria and analysis groups

Eligibility criteria

- Adults (aged ≥18 years) and adolescents (aged 12–17 years)
- One of the following:
  - ≥1 pegvaliase or sapropterin dihydrochloride prescription
  - ≥1 MNT prescription and ≥1 PKU diagnosis claim (ICD-10 code E70.0 or E70.1)
  - ≥2 PKU diagnosis claims (ICD-10 code E70.0 or E70.1)
- ≥12 months of CE in HealthVerity, including ≥12 months of follow-up after the index date

Analysis groups

Adults (N = 1721)
- Pegvaliase (n = 299)
- Sapropterin dihydrochloride ± MNT (n = 311)
- MNT only (n = 266)
- No record of treatment (n = 845)[a]

Adolescents (N = 405)
- Pegvaliase (n = 8)
- Sapropterin dihydrochloride ± MNT (n = 180)
- MNT only (n = 95)
- No record of treatment (n = 122)[a]

[a]Reasons for patients having no record may include no treatment, treatment with MNT that is not covered by insurance or is paid for out of pocket, or other reasons.
CE, continuous enrollment; ICD, International Classification of Diseases; MNT, medical nutrition therapy; PKU, phenylketonuria.

Statistical analysis

- Mean differences in annualized HRU between treatment groups were evaluated using Welch's t-test (statistical significance was set at $P < 0.05$)
- Annualized visits represent the number of visits an individual (or group of individuals) would be expected to have in 1 year, based on the observed data, where:
  - Annualized visits = (total number of visits / total first continuous enrollment [CE] duration) × 365.25
  - Total first CE duration is the continuous period within the study timeframe (May 24, 2018, to March 31, 2023) during which an individual remained enrolled in both medical and pharmacy benefits, starting from the first date of CE
- All analyses were conducted separately for adults and adolescents

Results

Demographics and characteristics

- Data from 1721 adults and 405 adolescents with PKU were identified (**Table 1**)
  - Most adults with PKU had no record of treatment (49.1%), while similar proportions of patients received sapropterin dihydrochloride ± MNT (18.1%), pegvaliase (17.4%), and MNT only (15.5%)
  - Sapropterin dihydrochloride ± MNT was the most common therapy among adolescents (44.4%), followed by no record of treatment (30.1%), MNT only (23.5%), and pegvaliase (2.0%)
  - Mean age was higher in adults with PKU with no record of treatment than in other adult treatment groups, while mean age was similar across treatment groups among adolescents
  - Most individuals were insured under Medicaid or commercial plans

Table 1. Demographics and characteristics

Demographic/characteristic	Adults (N = 1721)				Adolescents (N = 405)			
	Pegvaliase (n = 299)	Sapropterin dihydrochloride ± MNT (n = 311)	MNT only (n = 266)	No record of treatment (n = 845)	Pegvaliase (n = 8)	Sapropterin dihydrochloride ± MNT (n = 180)	MNT only (n = 95)	No record of treatment (n = 122)
Age, years								
Mean ± SD	31.0 ± 10.5	30.2 ± 10.3	36.7 ± 16.9	48.6 ± 18.7	16.0 ± 0.9	14.2 ± 1.7	14.2 ± 1.7	14.4 ± 1.8
Median (IQR)	29 (22.0–38.0)	28 (22.5–35.0)	32 (23.0–46.0)	50 (32.0–62.0)	16 (16.0–16.3)	14 (13.0–16.0)	14 (13.0–15.0)	14 (13.0–16.0)
Range, min–max	18–63	18–68	18–89	18–94	14–17	12–17	12–17	12–17
Sex								
Male	130 (43.5)	128 (41.2)	112 (42.1)	322 (38.1)	2 (25.0)	105 (58.3)	55 (57.9)	46 (37.7)
Female	169 (56.5)	183 (58.8)	154 (57.9)	523 (61.9)	6 (75.0)	75 (41.7)	40 (42.1)	76 (62.3)
Geographic region								
South	114 (38.1)	93 (29.9)	73 (27.4)	267 (31.6)	3 (37.5)	67 (37.2)	37 (38.9)	23 (18.9)
Midwest	69 (23.1)	87 (28.0)	56 (21.1)	178 (21.1)	2 (25.0)	45 (25.0)	22 (23.2)	31 (25.4)
Northeast	61 (20.4)	67 (21.5)	69 (25.9)	210 (24.9)	2 (25.0)	36 (20.0)	18 (18.9)	24 (19.7)
West	54 (18.1)	64 (20.6)	68 (25.6)	189 (22.4)	1 (12.5)	32 (17.8)	18 (18.9)	43 (35.2)
Unknown	1 (0.3)	0	0	1 (0.1)	0	0	0	1 (0.8)
Payer type								
Medicaid	90 (30.1)	97 (31.2)	125 (47.0)	352 (41.7)	5 (62.5)	103 (57.2)	63 (66.3)	58 (47.5)
Commercial	182 (60.9)	170 (54.7)	95 (35.7)	273 (32.3)	3 (37.5)	65 (36.1)	27 (28.4)	57 (46.7)
Medicare Advantage	6 (2.0)	8 (2.6)	16 (6.0)	137 (16.2)	0	0	0	0
Dual	21 (7.0)	34 (10.9)	29 (10.9)	75 (8.9)	0	12 (6.7)	2 (2.1)	5 (4.1)
Unknown	0	2 (0.6)	1 (0.4)	8 (0.9)	0	0	3 (3.2)	2 (1.6)

Data are n (%) unless otherwise specified. Percentages may not total 100% due to rounding.
IQR, interquartile range; MNT, medical nutrition therapy; SD, standard deviation.

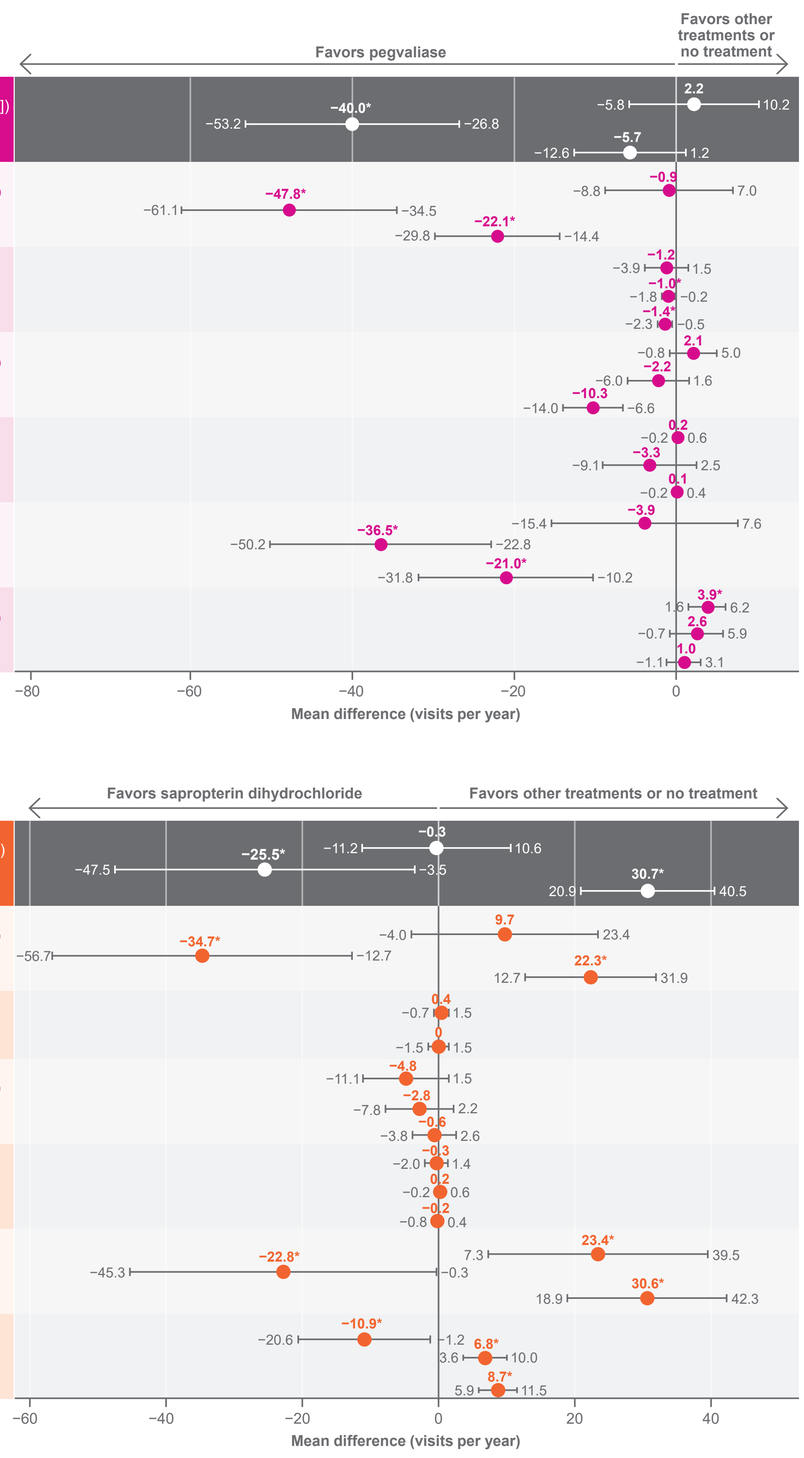
Annualized HRU

- Overall annualized HRU in adults treated with pegvaliase was significantly lower than in adults treated with MNT only, including a significantly lower mean number of medical, inpatient, and other visits (**Figure 2A**)
  - Length of inpatient stay was significantly lower in adults treated with pegvaliase (mean ± standard deviation [SD], 4.1 ± 10.8 days; median [interquartile range (IQR)], 1.8 [1.2–2.5] days) than in adults treated with MNT only (mean ± SD, 51.8 ± 101.5 days; median [IQR], 6.2 [1.4–34.8] days), with a mean difference of −47.7 days (95% confidence interval [CI], −71.2 to −24.2)
- Overall annualized HRU in adolescents treated with sapropterin dihydrochloride ± MNT was significantly lower than in adolescents treated with MNT only, including a significantly lower mean number of medical and other visits (**Figure 2B**)
  - Length of inpatient stay was significantly lower in adolescents treated with sapropterin dihydrochloride (mean ± SD, 7.5 [13.3] days; median [IQR], 1.2 [0.9–7.5] days) than in adolescents treated with MNT only (mean ± SD, 8.1 [18.4] days; median [IQR], 1.6 [0.9–6.1] days; with a mean difference of −0.6 days (95% CI, −12.1 to 10.9)
- Overall, both adults and adolescents receiving pharmacological therapy (pegvaliase or sapropterin dihydrochloride) had lower annualized HRU compared with MNT only (**Figure 2**)
- Adults treated with pegvaliase and adolescents treated with sapropterin dihydrochloride had higher mean pharmacy visits than individuals treated with MNT only or with no record of treatment (**Figure 2**)

Figure 2. Mean difference in annualized HRU by treatment in (A) adults with PKU (N = 1721) and (B) adolescents with PKU (N = 405)

A

Annualized visits, mean ± SD (median [IQR])	Pegvaliase (n = 299)	Sapropterin dihydrochloride ± MNT (n = 311)	MNT only (n = 266)	No record of treatment (n = 845)
Overall	45.3 ± 44.4 (33.7 [21.8–49.2])	43.1 ± 55.6 (27.5 [16.7–43.5])	85.3 ± 101.0 (41.6 [18.4–100.4])	62.9 ± 85.7 (30.4 [13.6–67.0])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				
Medical	28.3 ± 43.9 (16.2 [7.3–29.0])	29.2 ± 55.0 (13.3 [5.8–26.2])	76.1 ± 102.3 (29.5 [11.0–90.4])	50.4 ± 86.3 (17.4 [8.3–39.3])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				
Inpatient	0.9 ± 1.8 (0.5 [0.4–0.6])	2.1 ± 9.4 (0.4 [0.2–0.6])	1.9 ± 2.3 (0.8 [0.4–2.8])	2.3 ± 5.1 (0.8 [0.5–1.9])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				
Outpatient	15.5 ± 14.1 (11.7 [5.7–21.1])	13.4 ± 21.9 (7.4 [3.8–16.1])	17.7 ± 28.5 (8.4 [3.7–20.1])	25.8 ± 48.7 (12.2 [6.4–23.5])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				
Emergency room	1.4 ± 1.7 (0.9 [0.5–1.7])	1.2 ± 1.4 (0.7 [0.4–1.5])	4.7 ± 30.9 (0.9 [0.5–1.8])	1.3 ± 1.4 (0.8 [0.4–1.6])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				
Other	20.8 ± 51.0 (3.3 [1.0–12.1])	24.7 ± 60.9 (5.0 [1.2–14.3])	57.3 ± 93.6 (10.7 [4.9–55.8])	41.8 ± 85.3 (4.2 [0.9–26.0])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				
Pharmacy	21.5 ± 13.8 (18.8 [12.1–27.3])	17.6 ± 14.5 (13.5 [8.5–22.3])	18.9 ± 22.4 (11.2 [4.4–24.8])	20.5 ± 20.1 (14.8 [5.8–29.2])
Pegvaliase vs sapropterin dihydrochloride				
Pegvaliase vs MNT only				
Pegvaliase vs no record of treatment				



B

Annualized visits, mean ± SD (median [IQR])	Sapropterin dihydrochloride ± MNT (n = 180)	Pegvaliase (n = 8)	MNT only (n = 95)	No record of treatment (n = 122)
Overall	49.2 ± 58.0 (29.8 [18.7–50.5])	49.5 ± 9.2 (49.3 [43.7–55.6])	74.7 ± 99.8 (25.4 [13.9–74.7])	18.5 ± 27.0 (10.0 [4.2–21.4])
Saropterin dihydrochloride vs pegvaliase				
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				
Medical	36.5 ± 58.6 (14.8 [7.0–32.3])	26.8 ± 13.9 (22.7 [18.7–33.3])	71.2 ± 99.4 (24.3 [11.3–57.0])	14.2 ± 23.6 (7.6 [3.7–14.2])
Saropterin dihydrochloride vs pegvaliase				
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				
Inpatient[†]	1.3 ± 1.7 (0.4 [0.3–1.3])	–	0.9 ± 1.3 (0.5 [0.3–0.8])	1.3 ± 1.6 (0.6 [0.4–0.9])
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				
Outpatient	10.9 ± 11.0 (7.2 [4.2–12.7])	15.7 ± 7.4 (13.7 [9.9–18.8])	13.7 ± 23.0 (6.0 [2.9–3.0])	11.5 ± 15.6 (6.7 [3.3–11.5])
Saropterin dihydrochloride vs pegvaliase				
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				
Emergency room	0.9 ± 1.2 (0.5 [0.4–0.8])	1.2 ± 1.3 (0.7 [0.4–1.1])	0.7 ± 0.6 (0.6 [0.3–0.9])	1.1 ± 1.5 (0.6 [0.4–1.3])
Saropterin dihydrochloride vs pegvaliase				
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				
Other	35.2 ± 64.1 (8.1 [2.2–23.2])	11.8 ± 14.2 (4.4 [3.4–15.1])	58.0 ± 95.9 (11.9 [6.5–31.1])	4.6 ± 13.5 (1.1 [0.5–3.5])
Saropterin dihydrochloride vs pegvaliase				
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				
Pharmacy	16.6 ± 11.5 (13.4 [8.9–21.3])	27.5 ± 11.3 (27.8 [18.1–33.1])	9.8 ± 12.0 (4.3 [1.1–14.4])	7.9 ± 11.1 (4.0 [1.3–8.8])
Saropterin dihydrochloride vs pegvaliase				
Saropterin dihydrochloride vs MNT only				
Saropterin dihydrochloride vs no record of treatment				

*$P < 0.05$. Error bars are 95% CIs.
[†]A comparison between sapropterin dihydrochloride and pegvaliase for inpatient visits is not included in this figure as data were not available for the pegvaliase group. At the time of analysis, sapropterin dihydrochloride was the only pharmacological treatment approved in the US for the treatment of PKU in adolescents.[6]
Annualized visits calculated among individuals with records of each respective visit type. Overall visits: Includes medical and pharmacy visits. Other visits: Visit type could not be determined due to missing type of bill/place of service codes. Medical visits: Includes all visits except pharmacy visits.
CI, confidence interval; HRU, healthcare resource utilization; IQR, interquartile range; MNT, medical nutrition therapy; PKU, phenylketonuria.

Conclusion

- Findings suggest that adults and adolescents in the US with PKU treated with MNT only incur a substantial health economic burden compared with those receiving pharmacological treatment

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