Journal of Asthma and Allergy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

SHORT REPORT

Drug Patterns and Economic Costs Among Patients with Hereditary Angioedema

Emily Kutrieb[1], Derek Weycker[1], Montserrat Vera-Llonch[2], Arthur Zbrozek[3], Kevin Ottino[1], William R Lumry[4]

[1]Avalere Health, Washington, DC, USA; [2]Ionis Pharmaceuticals, Boston, MA, USA; [3]Ionis Pharmaceuticals, Carlsbad, CA, USA; [4]Allergy and Asthma Research Associates Research Center, Dallas, TX, USA

Correspondence: Derek Weycker, Avalere Health, 1201 New York Ave NW, Washington, DC, 20005, USA, Email derek.weycker@avalerehealth.com

Background/Objectives: This study explored real-world patterns of subcutaneous (SC) long-term prophylaxis (LTP), prescriptions for on-demand treatment (ODT), and treatment-related expenditures among patients with hereditary angioedema (HAE).

Methods: This study was conducted using a retrospective cohort design and US healthcare claims database (02/23/18–06/30/22). Study population included patients aged ≥12 years who initiated SC LTP with C1-esterase inhibitor (C1-INH-SC) or lanadelumab for HAE management. Study measures were evaluated from the date of LTP initiation through the last date of health plan enrollment or the study period. Study measures included LTP adherence (medication possession ratio [MPR]), LTP discontinuation (gap in drug supply ≥60 days), annualized number of ODT prescriptions, and annualized treatment-related expenditures (ie., ODT prescriptions and emergent care [all-cause hospitalizations and emergency department (ED) visits]). Measures were summarized using means, percentages, and 95% confidence intervals (CI).

Results: Study population included 196 patients (C1-INH-SC: N=65; lanadelumab: N=131); mean age was 39 years and 69% were female. During a mean follow-up of 19 months, MPR for LTP was 73% (CI: 68–77) and LTP discontinuation was 48% (41–55). Mean annualized number of ODT prescriptions was 3.8 (3.6–4.1) per patient, and mean annualized treatment-related expenditures totaled $209,547 (133,460–325,453) per patient, including $200,886 (124,792–317,983) for ODT prescriptions, $7,299 (3,408–12,214) for hospitalizations and $1,363 (859–1,959) for ED visits.

Conclusion: Despite the availability of SC LTP for the management of HAE, adherence was suboptimal, almost 50% of patients discontinued prophylaxis, and treatment-related expenditures were high. Notably, annualized expenditures for ODT prescriptions, hospitalizations, and ED visits averaged >$200,000, even after initiation of SC LTP.

Plain Language Summary: Hereditary angioedema (HAE) is a rare genetic condition typically involving recurrent and unpredictable attacks of swelling that often require reactive use of on-demand treatment (ODT). Since 2017, three agents have been approved for long-term prophylaxis (LTP) of HAE attacks, including two subcutaneous agents: C1 esterase inhibitor and lanadelumab. While two prior studies evaluated the real-world clinical and economic impact of these agents, attention was limited to patients who were adherent over an extended period and thus results were unreflective of effectiveness/costs among the full population of patients initiating LTP. The present study addressed this gap by exploring real-world patterns of subcutaneous LTP, prescriptions for ODT, and healthcare expenditures among all patients with HAE initiating subcutaneous LTP, including those who were and were not adherent. From a study population comprising 196 patients followed for 19 months (on average), almost 50% discontinued LTP and expenditures for ODT remained high (>$200,000/year). Collectively, study results demonstrated suboptimal effectiveness and considerable unmet need in the management of HAE.

Keywords: hereditary angioedema, clinical practice patterns, outcomes assessment, cost and cost analysis

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominant condition characterized by repeated episodes of nonpruritic, nonpitting, subcutaneous, or submucosal swelling without urticarial lesions.[1] Clinical events associated with HAE are called "attacks," and can involve multiple bodily areas, including hands, feet, intestinal wall, genitalia, face, tongue, or

https://doi.org/10.2147/JAA.S565239
Received: 24 October 2025
Accepted: 14 April 2026
Published: 3 May 2026

larynx. Swelling of the pharynx or larynx can cause life-threatening asphyxia. Attacks may start with a prodromal sensation of tingling that can be accompanied by the development of a nonpruritic wavy eruption known as erythema marginatum, which is followed by slowly progressive swelling that gradually subsides over 48–72 hours.[2] While HAE attacks can occur spontaneously, there are multiple triggers that can be associated with attack initiation (eg, stress/anxiety, use of certain drugs, minor trauma, surgery, and infection).[3]

Until recently, the management of HAE attacks was largely limited to prophylactic use of an intravenous C1 esterase inhibitor (IV-C1-INH) and/or reactive use of on-demand treatment (ODT).[4] Since 2017, three additional agents have been approved for the prevention of attacks in patients with HAE including subcutaneous C1-INH (SC-C1-INH),[5] subcutaneous lanadelumab,[6] and oral berotralstat.[7] Evidence on the real-world clinical and economic impact of long-term prophylaxis (LTP) with SC-C1-INH and/or lanadelumab has been reported in two published studies.[8,9] These studies, however, limited attention to patients with HAE who were adherent to LTP over an extended period of time, and thus study results do not reflect the effectiveness/costs of such agents among the full population of patients initiating LTP in clinical practice. Accordingly, a new study was undertaken to explore real-world patterns of LTP, prescriptions for ODT, and treatment-related healthcare expenditures among patients with HAE initiating SC-C1-INH or lanadelumab, including those who were and were not adherent with LTP.

Methods

Study Design and Data Sources

A retrospective observational cohort design was employed, and data (02/23/2018–06/30/2022; "Study Period") were obtained from the Merative MarketScan Research Databases (Commercial Claims and Encounters [CCAE] and Medicare Supplemental and Coordination of Benefits [MDCR] Databases). The CCAE Database includes healthcare claims and enrollment information from employer-sponsored commercial plans throughout the US that provide health benefits to working persons aged <65 years, including the employees as well as their spouses and dependents. The MDCR Database includes healthcare claims and enrollment information for Medicare-eligible retirees who enrolled in an employer-sponsored Medicare supplemental plan (and for which Medicare- and employer-paid amounts are available).

Medical (ie, facility and professional-service) claims include the dates/places of service, diagnoses, procedures, and quantity of services (professional-service claims). Outpatient pharmacy claims include the drug dispensed, dispensing date, dose, quantity dispensed, and therapy days. Medical and pharmacy claims also include amounts paid by health plans and patients to healthcare providers for services rendered. Selected demographic and eligibility information is available, and patient-level data can be arrayed to provide a longitudinal profile of healthcare services used by each plan member.

Ethical Approval

The study data source was de-identified prior to its release to study investigators, as set forth in the corresponding Data Use Agreement. Use of the study data source for health services research was fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects (45 CFR 46 §46.101); accordingly, Institutional Review Board (IRB) approval was not required.

Study Population

The study population comprised patients aged ≥12 years who initiated LTP with SC-C1-INH or lanadelumab between August 23, 2018 and June 30, 2022 ("identification period"). Initiation of LTP was designated based on the date of the first claim ("index date") with a corresponding code from the Healthcare Common Procedure Coding System (medical claims) or National Drug Code (pharmacy claims) during the identification period; and no such claims during the 6-month ("history") period immediately preceding the index date (Supplement Table 1). Patients without health plan enrollment during their history period were excluded from the study population as evidence on prior use of LTP was partially/fully unobservable. Qualifying patients were pooled into a single subgroup to increase the robustness of analyses; patients who initiated berotralstat during the identification period were not included due to small sample size and limited follow-up.

Study Variables

Study measures were ascertained from the date of LTP initiation through the date of health plan disenrollment or end of the study period, whichever occurred first, and included LTP adherence, LTP discontinuation, annualized number of ODT prescriptions, and annualized treatment-related expenditures. LTP adherence (ie., to agent first received) was defined using the medication possession ratio (MPR), ie., the ratio of total number of prophylaxis days to the total number of follow-up days. Prophylaxis days were tallied based on drug administrations from medical claims and dispensed prescriptions from outpatient pharmacy claims. For medical claims, each administration was assumed to correspond to four prophylaxis days for SC-C1-INH and fourteen prophylaxis days for lanadelumab. For pharmacy claims, prophylaxis days were determined based on days/quantity supplied.

LTP discontinuation (ie., of first agent received) was defined as a gap of ≥60 days in supply of drug[8]; alternative thresholds (ie., ≥30, ≥90 days) were also considered. Annualized treatment-related expenditures (2024 USD) were ascertained based on all-cause hospitalizations, all-cause emergency department (ED) visits, and ODT prescriptions (Supplement Table 2). Baseline characteristics of patients in the study population were ascertained during the 6-month history period, and included demographics (age, sex), comorbidity profile (identified based on ≥1 diagnosis code; Supplement Table 3), and use of ODT.

Statistical Analyses

Baseline characteristics were analyzed descriptively. Categorical variables were reported as percentages; continuous variables were reported using means and standard deviations (SDs). Study measures were summarized using means, incidence proportions, and corresponding 95% confidence intervals (CIs), which were calculated using techniques of non-parametric bootstrapping. Number of ODT prescriptions and treatment-related expenditures were annualized using a population-based approach.

Results

A total of 411 patients aged ≥12 years had evidence of LTP with SC-C1-INH or lanadelumab during the identification period. Among the 411 patients, 270 were continuously enrolled during the 6-month history period, and among these patients, 196 also had no evidence of LTP during the history period (ie., were presumed to initiate LTP on their index date), and were included in the study population. Among the 196 patients, 131 (67%) first initiated LTP with lanadelumab and 65 (33%) with SC-C1-INH. Mean (SD) age of the study population was 39 (15) years, and 69% were female (Table 1). The most common comorbidities were metabolic disorders (32%), obesity (24%), and respiratory disease (19%); 77% of patients had a history of ODT use.

Table 1 Baseline Characteristics

	Study Population (N=196)
Initial LTP Agent, n (%)	
C1-esterase inhibitor (C1-INH-SC)	65 (33.2)
Lanadelumab	131 (66.8)
Age (years)	
Mean (SD)	39.1 (15.3)
Groups, n (%)	
12-17	8 (4.1)
18-34	69 (35.2)
35-44	49 (25.0)
45-54	35 (17.9)

(*Continued*)

Table 1 (Continued).

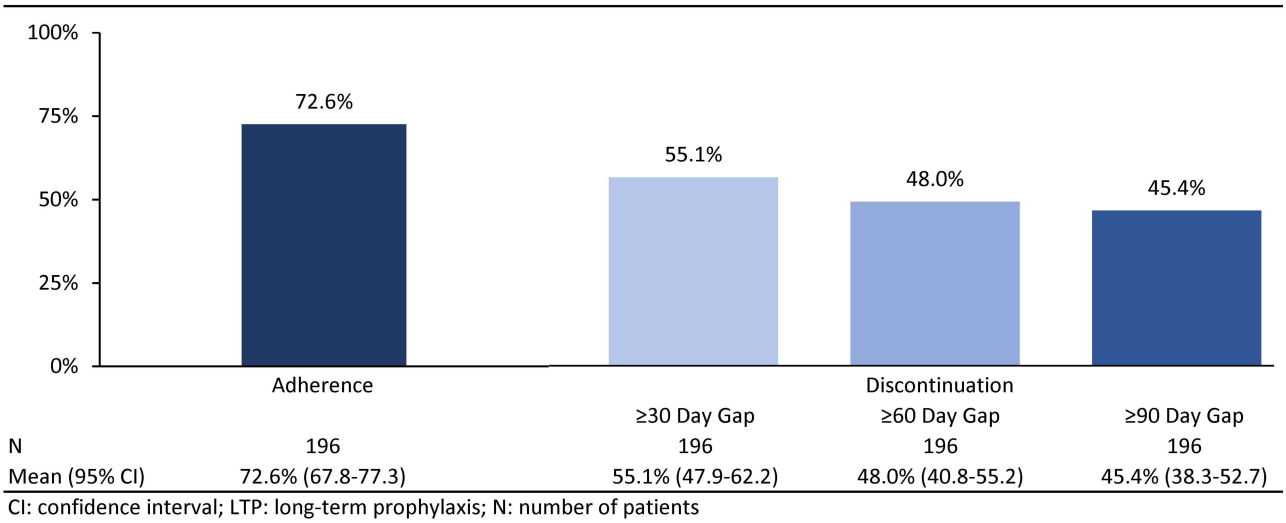
	Study Population (N=196)
55-64	28 (14.3)
≥65	7 (3.6)
Sex, n (%)	
Female	136 (69.4)
Male	60 (30.6)
Comorbidity Profile, n (%)	
Cardiovascular disease	21 (10.7)
Diabetes	19 (9.7)
Immunosuppressive conditions/treatments	15 (7.7)
Liver disease	9 (4.6)
Metabolic disorders	62 (31.6)
Neurologic disorders	10 (5.1)
Obesity (BMI >40)	47 (24.0)
Osteoarthritis	13 (6.6)
Respiratory disease	37 (18.9)
Use of ODT, n (%)	
Any ODT	150 (76.5)
Berinert	32 (16.3)
Cinryze	40 (20.4)
Icatibant	102 (52.0)
Kalbitor	8 (4.1)
Ruconest	23 (11.7)

Abbreviations: BMI, body mass index; LTP, long-term prophylaxis; ODT, on-demand treatment; SD, standard deviation.

During a mean (SD) follow-up of 19 (13) months, mean MPR for LTP was 73% (95% CI: 68–77) (Figure 1). Based on a 60-day gap in drug supply, the percentage of patients who discontinued LTP was 48% (41–55); when using alternative thresholds, discontinuation was 55% (48–62) based on a 30-day gap and 45% (38–53) based on a 90-day gap. Mean annualized number of ODT prescriptions was 3.8 (3.6–4.1) per patient (Figure 2). Mean annualized treatment-related expenditures totaled $209,547 (133,460–325,453) per patient, including $200,886 (124,792–317,983) for ODT prescriptions, $7,299 (3,408–12,214) for hospitalizations, and $1,363 (859–1,959) for ED visits.

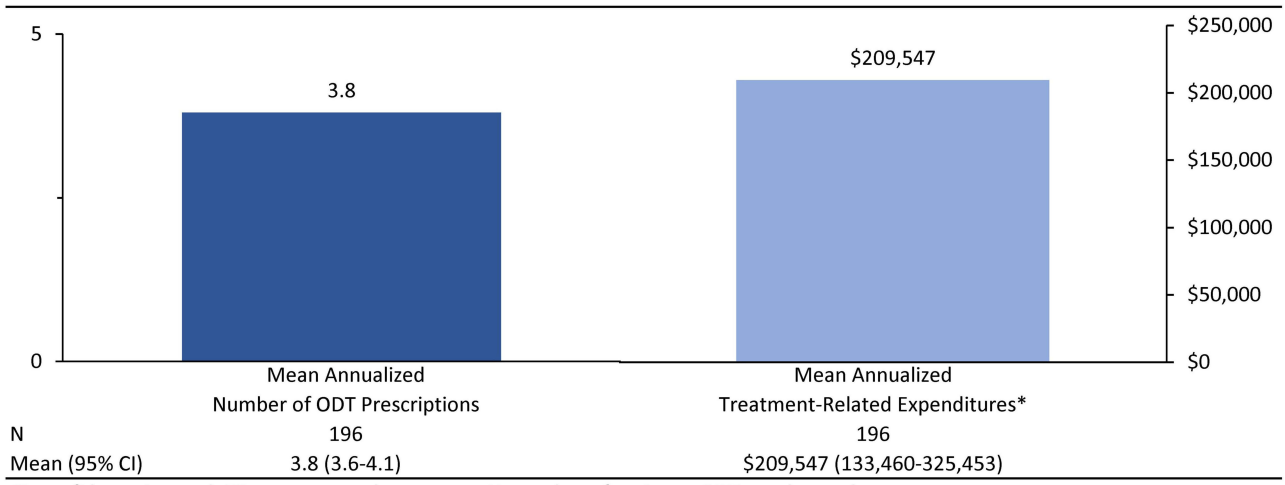
Discussion

Using data from a large healthcare claims repository, we evaluated drug patterns and treatment-related expenditures among patients with HAE who initiated LTP with SC-C1-INH or lanadelumab. Study findings indicate that, while newer LTP agents are now available, adherence levels among the study population were not optimal and the percentage of patients who discontinued LTP was high during the follow-up period (mean duration = 19 months). On an overall basis, mean LTP adherence was less than 75%, which based on commonly cited thresholds, indicates "poor" or "inadequate" adherence among the study population.[10–16] Moreover, LTP discontinuation ranged from 45–55% (depending on the required gap in drug supply), suggestive of low persistency rates based on published research.[17–20] Study findings also indicate that treatment-related healthcare expenditures—especially for ODT—were high following initiation of LTP. Based on all patients, including those who did and did not fill prescriptions for ODT, the mean number of filled prescriptions was 3.8, corresponding to over $200,000 in annualized treatment-related expenditures. Taken collectively, the findings from this study suggest considerable unmet need in the management of HAE.



CI: confidence interval; LTP: long-term prophylaxis; N: number of patients

Figure 1 LTP adherence and discontinuation.



CI: confidence interval; ED: emergency department; N: number of patients; ODT: on-demand treatment

*Mean annualized treatment-related expenditures comprise ODT ($200,886 [124,792-317,983]), all-cause hospitalizations ($7,299 [3,408-12,214]), and all-cause ED visits ($1,363 [859-1,959])

Figure 2 Mean annualized number of ODT prescriptions and treatment-related expenditures.

In a 2023 retrospective study using the Merative MarketScan Databases (01/01/2018–06/30/2022), Shah et al evaluated healthcare expenditures among patients with HAE who initiated LTP with lanadelumab.[8] The study population was limited to patients who initiated lanadelumab, did not have a gap in drug supply of ≥60 days during an 18-month follow-up period, and were continuously enrolled during the 6-month history period and the entire follow-up period. While, among the 54 lanadelumab-persistent patients in the study population, mean HAE treatment expenditures—including LTP, ODT/short-term prophylaxis, and supportive care—decreased from months 0–6 ($377,076) to months 13–18 ($286,074). Following initiation of lanadelumab, 6-month expenditures for ODT and short-term prophylaxis ranged from $38,000–$59,000.

In another 2023 retrospective study using the Merative MarketScan Databases (12/23/2016–03/31/2021), Reidl et al evaluated healthcare expenditures among patients with HAE who initiated LTP with lanadelumab or SC-C1-INH.[9] The study population was limited to patients who had ≥180 days of continuous LTP. Among the 47 lanadelumab-persistent patients and SC-C1-INH-persistent patients, all-cause hospitalizations and all-cause ambulatory encounters decreased following initiation of LTP as did the use of ODT. Total annualized healthcare

https://doi.org/10.2147/JAA.S565239

expenditures (2020 USD)—including hospitalizations, ambulatory encounters, and pharmacy—increased by $165,000–$336,000, most of which was attributable to pharmacy expenditures.

As noted above, however, the authors of these studies limited attention to patients who were persistent with LTP, which likely yielded results more reflective of those from a controlled clinical trial versus an uncontrolled real-world setting that is subject to the vagaries of clinical practice. LTP discontinuation is an important real-world phenomenon and should be considered in evaluating drug effectiveness (vs efficacy) and associated outcomes and costs. Patients not persistent with LTP may be systematically different in terms of their observed/unobserved characteristics such as disease severity, attack profile, and economic burden. Moreover, evidence suggests that this issue is not "analytically ignorable"; in the study by Shah et al, 33% of patients initiating lanadelumab were excluded from the study population because they were not persistent with therapy for at least 18 months.

While healthcare claims databases provide information on large numbers of patients with specific diagnoses who receive care for specific conditions, several limitations from the use of such databases should be noted. Patients with healthcare claims for LTP were assumed to have HAE since a unique diagnosis code for HAE does not currently exist. Prescriptions for ODT should not be assumed to equate to use of ODT due to, for example, stockpiling. Patients who first initiated LTP with berotralstat were not included due to small sample size and limited follow-up. Patients with certain types of public health insurance (eg, Medicaid) and those without health insurance are not represented in the study database; caution should be exercised when generalizing these study results to other populations and settings. Finally, reasons for discontinuation of LTP and suboptimal adherence to LTP are unobservable in the study data source. It thus is unknown to what extent LTP discontinuation/low adherence were attributable to lack of effectiveness, adverse events, or other factors. Better understanding the precise reasons underlying real-world treatment patterns is critical for improving patient care and outcomes, and future research in this area is needed.

Conclusions

Despite the availability of newer LTP agents, adherence was not optimal and ~50% of patients discontinued prophylaxis. Notably, annualized expenditures for ODT prescriptions, hospitalizations, and ED visits averaged >$200,000, even after initiation of LTP, thus demonstrating considerable unmet need in the management of HAE.

Prior Presentation

Findings from this study were presented at ACAAI 2024 (Boston, MA; October 24–28, 2024) as a poster presentation. The poster's abstract was published under "Oral Abstracts" in Annals of Allergy, Asthma & Immunology: https://doi.org/10.1016/j.anai.2024.08.106.

Data Sharing Statement

The study data sources are proprietary, provided by a third-party vendor via a license agreement with Avalere Health, and the authors do not have permission to disseminate the data without approval of the vendor. Inquiries regarding acquisition of the study data sources may be directed to the data vendor (Merative).

Acknowledgments

Ellen Dukes participated in the conception, design, and conduct of this study as well as manuscript preparation during her tenure at Avalere Health. Assistance with manuscript copyediting and preparation of tables/figures was provided by Lisa Abramovitz and Mary Cecil, who are employed by Avalere Health.

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.

Funding

Funding for this research was provided by Ionis Pharmaceuticals to Avalere Health and William R. Lumry.

Disclosure

Derek Weycker and Kevin Ottino are employed by Avalere Health. Emily Kutrieb was employed by Avalere Health during the design and conduct of this study. Montserrat Vera-Llonch is employed by Ionis Pharmaceuticals. Arthur Zbrozek was employed by Ionis Pharmaceuticals during the design and conduct of this study. William R. Lumry is employed by the Allergy and Asthma Research Associates Research Center; has consulting arrangements with Astria, BioCryst, Biomarin, CSL Behring, Express Scripts/CVS, Intellia, Kalvista, Magellan, Optum, Pharming, Pharvaris, and Shire/Takeda; participated in Speakers' bureaus with BioCryst, CSL Behring, Pharming, Shire/Takeda, Grifols, Astra Zeneca, Sanofi/Regeneron, and GSK; has grants/research support from Astra Zeneca, Astria, BioMarin, CSL Behring, Grifols, Ionis, Kalvista, Lilly, Novartis, Pharvaris, Shire/Takeda, Teva, and Up Stream Bio; and has board membership with Adarx, the US Hereditary Angioedema Association Medical Advisory Board and DFW Metroplex Allergy Society.

References

1. Ferrante G, Scavone V, Muscia MC, et al. The care pathway for children with urticaria, angioedema, mastocytosis. *World Allergy Organ J*. 2015;8(1):5. doi:10.1186/s40413-014-0052-x
2. Zuraw BL. Clinical practice. hereditary angioedema. *N Engl J Med*. 2008;359(10):1027–1036. doi:10.1056/NEJMcp0803977
3. Keller S. Hereditary angioedema triggers. *Healthline*. 2022. Available from: https://www.healthline.com/health/hereditary-angioedema/monitoring-triggers. Accessed January 8, 2025.
4. Lumry WR. Hereditary angioedema: the economics of treatment of an orphan disease. *Front Med*. 2018;5:22. doi:10.3389/fmed.2018.00022
5. Prescribing information: C1-INH. Available from: https://labeling.cslbehring.com/PI/US/HAEGARDA/EN/HAEGARDA-Prescribing-Information.pdf. Accessed September 12, 2024.
6. Prescribing information: lanadelumab. Available from: https://www.shirecontent.com/PI/PDFs/TAKHZYRO_USA_ENG.pdf. Accessed September 12, 2024.
7. Prescribing information: berotralstat. Available from: https://www.biocryst.com/wp-content/uploads/ORLADEYO_USPI.pdf. Accessed September 12, 2024.
8. Shah CH, Princic N, Evans KA, Schultz BG. Real-world changes in costs over time among patients in the United States with hereditary angioedema on long-term prophylaxis with lanadelumab. *J Med Econ*. 2023;26(1):871–877. doi:10.1080/13696998.2023.2232260
9. Riedl MA, Hinds DR, Prince PM, et al. Healthcare utilization of patients with hereditary angioedema treated with lanadelumab and subcutaneous C1-inhibitor concentrate. *Allergy Asthma Proc*. 2023;44(4):275–282. doi:10.2500/aap.2023.44.230026
10. Rolnick SJ, Pawloski PA, Hedblom BD, et al. Patient characteristics associated with medication adherence. *Clinical Medicine & Research*. 2013;11(2):54–65. doi:10.3121/cmr.2013.1113
11. Halpern R, Agarwal S, Dembek C, et al. Comparison of adherence and persistence among multiple sclerosis patients treated with disease-modifying therapies: a retrospective administrative claims analysis. *Patient Prefer Adherence*. 2011;5:73–84. doi:10.2147/PPA.S15702
12. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40(7–8):1280–1288. doi:10.1345/aph.1H018
13. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health Aff*. 2011;30(1):91–99. doi:10.1377/hlthaff.2009.1087
14. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Medication adherence and use of generic drug therapies. *Am J Manag Care*. 2009;15(7):450–456.
15. Sedjo RL, Cox ER. Lowering copayments: impact of simvastatin patent expiration on patient adherence. *Am J Manag Care*. 2008;14(12):813–818.
16. Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007;10(1):3–12. doi:10.1111/j.1524-4733.2006.00139.x
17. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. *Neuropsychiatr Dis Treat*. 2014;10:1543–1569. doi:10.2147/NDT.S65721
18. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB. Comparing adherence and persistence across 6 chronic medication classes. *J Manag Care Pharm*. 2009;15(9):728–740. doi:10.18553/jmcp.2009.15.9.728
19. Lee DSU, Lee H. Adherence and persistence rates of major antidiabetic medications: a review. *Diabetol Metab Syndr*. 2022;14(1):12. doi:10.1186/s13098-022-00785-1
20. Muntner P, Yun H, Sharma P, et al. Ability of low antihypertensive medication adherence to predict statin discontinuation and low statin adherence in patients initiating treatment after a coronary event. *Am J Cardiol*. 2014;114(6):826–831. doi:10.1016/j.amjcard.2014.06.009