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Primary medication nonadherence calculation method specifications impact resulting rates

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ABSTRACT

Background: Previous literature has illustrated a wide range of primary medication nonadherence (PMN) rates due to inconsistent calculation methods and parameters, but the impact of parameter specifications on PMN rates has not been assessed.

Objectives: The objective of this study was to evaluate the impact of lookback window (LBW), duplicate window (DW), and fill window (FW) specifications on PMN rates in patients prescribed specialty self-administered oncology medications.

Methods: This was a single-center, retrospective cohort analysis. Patients receiving a new electronic specialty oncology prescription January–December 2018 were included; excluded if re-routed to an external pharmacy within 2 days, fell within a DW, or cancelled within a FW. Twenty-four methods were used to calculate PMN based on combinations of the following parameters: (i) absence of prior specialty self-administered oncology medication fill within LBW (90, 180 days); (ii) absence of a duplicate prescription within DW (2, 7, 30 days); and (iii) sold status within FW (14, 30, 60, 90 days). For each method, PMN was calculated as the number of unsold prescriptions within the FW divided by all eligible prescriptions.

Results: We evaluated 4,482 prescriptions, resulting in PMN ranging from 16% to 23%. Patients were commonly male (53%) and white (83%), with a median age of 64 years (interquartile range, IQR, 54, 72). Increasing the LBW from 90 to 180 days resulted in exclusion of 72 (2%) prescriptions and minimally impacted PMN rates. Most duplicate prescriptions (87%) occurred within two days of original prescription and PMN rates were minimally affected by DW. Most fulfilled prescriptions were filled within FW 30 days, 98% with a method of LBW 180, DW 2, and FW 30. Adjusting the FW consistently impacted PMN rates.

Conclusions: Because various PMN definitions can significantly impact results, a thorough explanation of all parameter specifications should be reported in research using PMN.

Introduction

Adherence to prescribed medications is necessary to achieve benefits of therapy. Medication non-adherence increases healthcare costs and leads to worse patient outcomes in patients with chronic conditions.[1–4] Adherence begins with procuring the prescribed medication from a pharmacy. Primary medication nonadherence (PMN) occurs when a new medication is prescribed, but the patient does not procure it (or an appropriate alternative) within an acceptable timeframe.[5] Recently, there has been an increase in research evaluating PMN, likely catalyzed by the improved ability to better track prescription data through electronic prescribing.[5,6] PMN is distinct from secondary nonadherence, defined as the rate at which a medication is refilled after an initial prescription fill,[5] and prescription abandonment, defined as the rate a new or refill prescription is filled by a pharmacy but not claimed by the patient.[5] Barriers to prescription fulfillment are often amplified in patients prescribed specialty medications because of complex insurance authorization processes and treatment affordability concerns.[7] Understanding PMN would offer unique insights regarding barriers patients face when obtaining a new specialty prescription.

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Rates of PMN range from 0.5% to 75% in previous literature[5,8] and methods for calculating PMN differ greatly.[5,6,8,9] Study designs vary by drug and/or disease state of interest, data source (administrative claims, patient-reported, pharmacist-reported), sample size, and specifics of the PMN calculation. Electronic prescribing allows for better use of administrative claims data, and a growing number of studies explore the association between an electronic prescription (e-prescription) and a pharmacy claim or lack thereof. PMN calculations using administrative claims data vary in specification of a lookback window (LBW, minimum time period required to define a "new" prescription), duplicate window (DW, duration of time to define a "duplicate" prescription), fill window (FW, duration of time to identify a "fill event"), and therapeutic equivalence or appropriate alternative. Definitions for LBW, DW, and FW are listed in Table 1. To the best of our knowledge, the impact of these calculation specifications has not been described. Though recent efforts by the Pharmacy Quality Alliance (PQA) to standardize the PMN calculation provide guidance for a subset of chronic conditions,[5] variability in PMN calculation remains. Moreover, interpreting historical PMN rates without understanding how differences in calculation methods can impact these rates is challenging.

The primary objective of this study was to evaluate the impact of LBW, DW, and FW specifications on PMN rates for patients with specialty self-administered oncology prescriptions sent to an integrated specialty pharmacy for fulfillment. Measuring the impact of the varying specifications is needed to better interpret historical PMN results and derive a calculation that accurately identifies patients at risk for or experiencing PMN to specialty medications.

Methods

This was a single-center, retrospective cohort analysis of patients with an electronic prescription for a new specialty self-administered oncology medication sent from Vanderbilt University Ingram Cancer Center to Vanderbilt Specialty Pharmacy between January and December 2018. As no clear definition of a specialty medication exists, specialty pharmacists created a list of self-administered oncology medications based on cost and difficulty to access outside of a specialty pharmacy setting, similar to previous studies[10] (Appendix A). The health-system integrated specialty pharmacy receives most of the specialty oral oncology medication prescriptions prescribed within the institution, completes the financial assistance process to ensure medication access, then either fills the medication internally or triages the prescription to an external specialty pharmacy if required by the manufacturer or payer or requested by the patient.

Table 1
Parameter definitions for primary medication nonadherence (PMN).

Parameter	Definition
Lookback window (LBW)	Minimum length of time prior to the index prescription in which a patient may revert to naïve status, and thus be considered a "new" prescription and a potential instance of PMN. Determined by previous fill within the specified timeframe.
Duplicate window (DW)	Duration of time within which two sequential prescriptions for the same medication or therapeutic equivalent can be considered duplicate. Sequence of prescribed dates in a row without an intervening dispensation, cancellation, or transfer event.
Fill window (FW)	Duration of time within which a fill event of an eligible prescription needs to occur in order for the prescription to not be considered a case of PMN.
PMN-eligible prescription	No fill of any specialty self-administered oncology medication in specified LBW. No prescription duplication sent within two days of prescribing event. No prescription re-route to external specialty pharmacy within two days of prescribing event. No prescription cancellation within two days of prescribing event.

For a prescription to be PMN-eligible, the patient must not have filled the medication or a therapeutic equivalent previously. However, due to the limitations of the electronic health record (EHR), the full medical history of a patient may not be available or appropriate to assess. Therefore, to consistently determine PMN-eligibility, we defined a 'new' prescription as the absence of a prior filled prescriptions for the medication within a specified LBW. We adjusted the length of the LBW as a means of varying the subset of prescriptions eligible for PMN. Prescriptions were not considered PMN-eligible if they were re-routed to an external pharmacy within two days of issuance, were sent within a specified DW, or were cancelled within a specified FW. Prescriptions may be cancelled (i.e., made no longer a valid or fillable prescription) by the pharmacist at a patient's or provider's request. Table 1 further defines LBW, DW, and FW as well as PMN-eligible prescription. This study was approved by the Vanderbilt University Institutional Review Board.

Data collection

Prescribing data were collected from the EHR and compared with the health-system's specialty pharmacy dispensing database. Because medication names may appear differently between these systems and the prescribing and dispensing systems do not otherwise share a reliable common medication terminology, we developed a list of potential medication names as they may appear in the EHR and dispensing database to create mapping between the two. Prescriptions were cross-referenced with prescriber specialty and excluded if there was a reasonable assumption the prescription was for a non-oncology condition (such as everolimus for transplant patients). For each eligible prescription, we collected patient age and gender, medication name and therapeutic class, and prescription date from the EHR; prescription outcome (cancelled, filled, not filled) and sold date (if applicable) were collected from the pharmacy claims database.

Primary medication nonadherence calculations

PMN was defined as lack of a fill event for the prescribed medication or a therapeutic equivalent within a specified FW. The prescription was considered filled when the prescribed medication had a completed claim with a sold date within the FW. We defined therapeutic equivalence as any specialty oncology medication on the developed list (Appendix A). PMN rate was calculated by dividing the number of prescriptions that did not have a fill event by the total number of PMN-eligible prescriptions sent to the internal specialty pharmacy during the study period.

Twenty-four methods were used to calculate PMN based on combinations of the following parameters: (i) absence of prior self-administered oncology medication fill within LBW (90, 180 days); (ii) absence of a duplicate prescription within DW (2, 7, 30 days); and (iii) prescription sold date within FW (14, 30, 60, 90 days) (Fig. 1). These parameters were applied to prescriptions in sequential order: LBW, then DW, then FW. A prescription was considered PMN-eligible after application of LBW, DW criteria and removal of cancelled prescriptions. For each method, PMN rate was computed as the number of prescriptions not dispensed within the FW (numerator) divided by all PMN-eligible prescriptions (denominator). These parameter specifications were selected based on literature review of previous PMN calculation methods and clinical practice experience.

Results

We evaluated 4,482 prescriptions from 1,422 unique patients. Most patients were male (53%) and white (83%), with a median age of 64 years (interquartile range, IQR 54, 72). Common medication classes included alkylating agents (13%), Janus associated kinase inhibitors

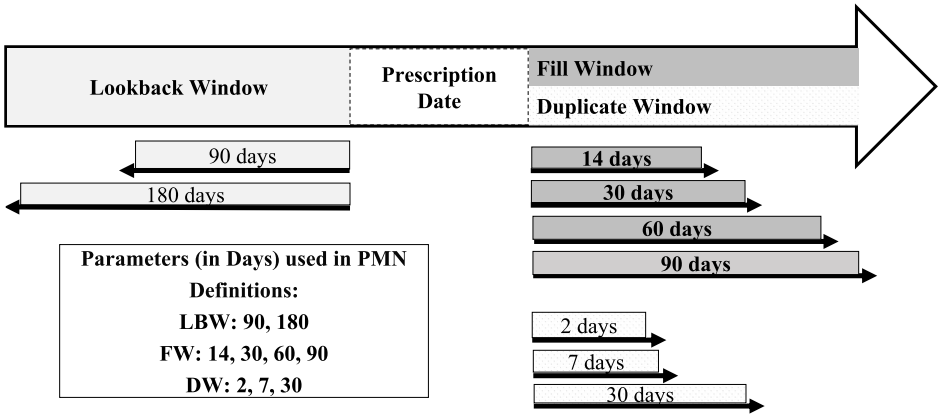

Fig. 1. Twenty-four Specification of Parameters for Primary Medication Nonadherence (PMN) Calculations.
This figure describes the specifications used for PMN calculations. Two time periods were used to evaluate the Lookback Window (LBW), shown in light grey: 90 and 180 days. Three time periods were used to evaluate the Duplicate Window (DW), shown in white with dots: 2, 7, and 30 days. Lastly, four time periods were used to evaluate the Fill Window (FW), shown in dark grey: 14, 30, 60, and 90 days.

(10%), and vascular endothelial growth factor inhibitors (9%). The 24 methods yielded PMN rates ranging from 16% to 23% (Fig. 2), also visualized in Fig. 3.

Increasing the LBW from 90 to 180 days excluded an additional 72 (2%) prescriptions and had minimal impact on PMN rates. Most duplicate prescriptions (87%) were recorded within two days of the original prescription date, while only 4% of duplicate prescriptions were received after 30 days. PMN rates were slightly affected by DW. Using LBW 180 days and FW 30 days, PMN rates were 20%, 18%, and 16% at DW 2, 7, and 30, respectively.

Few prescriptions were cancelled within any FW: 6 prescriptions using LBW 90 days and 4 using LBW 180 days. Most prescriptions with a fill were filled within 30 days, for example 99% with a method of LBW 180, DW 2 (Fig. 3). Adjusting the FW consistently impacted PMN rates, with the largest difference occurring between FW of 14 vs. 30 days. Holding LBW at 180 and DW at 2 days, rates of PMN were 23%, 20%, 19%, and 19% with FW 14, 30, 60, and 90 days, respectively. Using the PQA-endorsed PMN calculation (i.e., LBW 180, DW 30, and FW 30) resulted in the lowest rate of PMN among all 24 methods (16%). Reducing the FW to 14 days produced the highest rate of PMN (23%) for both LBW 90 and 180 with a DW of 2 days.

Discussion

Our study demonstrates that PMN rates differ greatly depending on the parameter specifications used in the calculation. As there is substantial variability in how PMN is defined in literature, our study findings warrant caution when interpreting the results. Our major findings suggest that lower PMN rates are observed with longer DW and FW windows, while adjusting the LBW has minimal influence. Researchers can infer that studies using a longer DW and/or FW windows are likely to have lower PMN rates, allowing for better comparison and evaluation amongst studies assessing PMN. Efforts to standardize PMN methodology for certain chronic medications have helped advance research with a more consistent definition of PMN.[5,6,9] However, to our knowledge, this is the first study to systemically evaluate the impact of varying parameter specifications on PMN rates.

Prescription procurement is the first step to medication adherence and is essential to achieve therapeutic benefit. The growing number of novel specialty medications provide an opportunity for patients with complex diseases to improve their quality of life and in some cases cure their disease.[11–13] However, barriers to medication access are pervasive and multifaceted within this high-cost area of pharmacy.[7,14] Results of this study are helpful to better understand PMN calculation parameters as more research on rates and reasons for PMN within specialty pharmacy is expected to be performed.

LBW[a] (days)	Rxs[b] in LBW[a] (N)	DW[c] (days)	Duplicate Rxs[b] (N)	Cancelled Rxs[b] (N)	Eligible Rxs[b] (N)	Rate of PMN[d] in FW[e]			
						14 days N (%)	30 days N (%)	60 days N (%)	90 days N (%)
90	3161	2	260	6	1055	240 (23%)	204 (19%)	196 (19%)	196 (19%)
		7	284	6	1031	216 (21%)	180 (17%)	172 (17%)	172 (17%)
		30	304	6	1011	196 (19%)	160 (16%)	152 (15%)	152 (15%)
180	3233	2	245	4	1000	230 (23%)	194 (19%)	188 (19%)	188 (19%)
		7	268	4	977	207 (21%)	171 (18%)	165 (17%)	165 (17%)
		30	286	4	959	189 (20%)	153 (16%)	147 (15%)	147 (15%)

[a] LBW: Lookback window; [b]Rx: prescription; [c]DW: Duplicate window; [d]PMN: primary medication nonadherence; [e]FW: fill window

Fig. 2. Primary Medication Nonadherence (PMN) Results by Specification of Parameters.
Results of the 24 methods are shown. Specifications were applied in a stepwise fashion: lookback window (LBW), duplicate window (DW), then fill window (FW). The number of prescriptions considered eligible for PMN after applying LBW and DW is shown prior to the PMN rate by FW. The time period for each specification is noted within the cell, with days increasing as you move down (LBW, DW) or to the right (FW). Rates of PMN are shown after applying LBW, DW, and FW specifications.

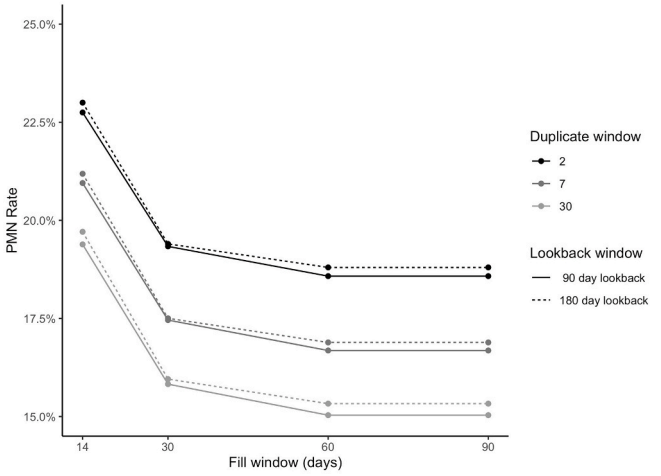

Fig. 3. Lookback, Duplicate and Fill Window Parameter Effects on Primary Medication Nonadherence (PMN) Rates.
Effects of the 24 PMN methods are graphically depicted. PMN rate is represented on the y-axis and FW on the x-axis. Minimal differences in PMN rates were seen when adjusting the LBW from 90 (represented by a solid line) to 180 days (represented by a dotted line). Increasing the DW led to overall lower rates of PMN with a DW of 2 days (black) having the highest rate of PMN, followed by 7 days (dark grey) and 30 days (light grey). Expanding the FW also reduced PMN rates, most notably between 14 and 30 days.

Lookback window (LBW)

The LBW is used to assess whether a prescription may be considered a new start. The newness of a prescription is an important aspect of PMN methodology that distinguishes it from prescription abandonment, which may refer to either a new or refill prescription. The LBW allows researchers to analyze only those patients who are prescribed a certain medication for the first time, when patients most commonly experience issues with accessing medications due to insurance approval requirements, affordability, or even identifying the appropriate specialty pharmacy to fill the prescription. These potential barriers are unique to the first prescription of a medication, emphasizing the necessity of an LBW when calculating PMN.[15] Additionally, prescription access issues are common with specialty prescriptions because of their high cost and often complex approval process.[14]

Though our results demonstrated a small difference in PMN rates between LBW 90 and 180, increasing the LBW permitted identification of more prescriptions that would have been inappropriately considered 'new.' Previous research describes LBWs ranging from 180 days[5,16,17] to two years,[18] and PQA endorses a LBW of 180 days.[5] Although we did not evaluate a LBW of greater than 180 days, a longer LBW might further improve the ability to identify a 'new' prescription and therefore a LBW of 180 days or greater is preferable if prescription fill data is available.

Duplicate window (DW)

A prescription may be generated more than once due to prescriber error, a pharmacy change, or a medication or dose change. We found that most duplicate prescriptions were sent close to the date of the original prescription (87% within two days). The prompt issuance of duplicate prescriptions seen in our study may be due to integrated specialty pharmacists quickly identifying problems with the first prescription, particularly if use of a different specialty pharmacy was required, if medication dose or duration was not accurate or if a different medication was preferred for financial or clinical reasons.

Though previous studies have used the PQA-endorsed DW of 30 days, few have discussed the consideration or timing of a duplicate window.[5,9] Based on our findings, 30 days is likely an appropriate interval to assess for duplicate prescriptions and shortening the DW may falsely elevate PMN rates. However, lengthening the DW might be appropriate for prescriptions written in specialty diseases that have significant access barriers as pharmacy staff may try to obtain insurance approval for greater than 30 days, necessitating medication changes and potential duplicate prescriptions sent more than 30 days after the original prescription.

Fill window (FW)

Our study suggests that adjusting the FW has the greatest impact on PMN rates regardless of LBW and DW specifications. Fig. 3 illustrates the measurable difference in PMN rates when increasing the FW from 14 to 30 days; however, this difference mostly leveled off between 30 and 90 days (Fig. 4). Almost all filled prescriptions had a fill event within the PQA-endorsed criteria of 30 days, which seems appropriate for most therapeutic classes. A FW shorter than 30 days may be appropriate for assessing PMN post-discharge,[19] but is unlikely to provide an accurate reflection of patient behavior for chronic medications. Several studies have used FW up to one year from the date of prescription.[20–23] Extending the FW to this degree calls into question the ongoing appropriateness and utility of the original prescription.

Therapeutic equivalence and alternative prescriptions

In PMN calculation methodology, it is important to define and include 'therapeutic equivalence' or appropriate alternative medications. This term is used to identify a different prescription written for the same indication and therefore an appropriate substitute for the original prescription in the LBW, DW, or FW. When applied to the LBW, including appropriate substitutions helps to identify 'new' prescriptions as described above. Including appropriate substitutions in the DW and FW accounts for intentional changes to the original prescription due to factors such as insurer requirements, new clinical information, or patient/provider decision.

We defined therapeutic equivalence as any specialty oncology medication since prescription substitution is rare within oncology. Several previous studies using PMN omit the description of therapeutic equivalence. Where described, therapeutic equivalence is commonly a

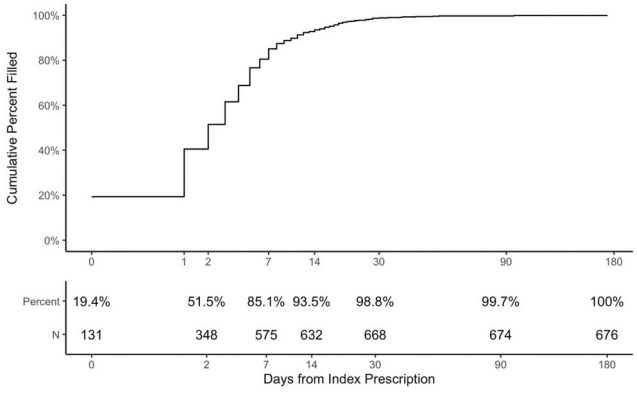

Fig. 4. Time to Prescription Fill Event.
Using an LBW of 180 days and a DW of 2 days, there were 1,000 prescriptions eligible for a primary medication nonadherence (PMN) evaluation, and of those, 676 had a fill event occur within the span of the study period. The figure above illustrates the impact that increasing or decreasing the length of the FW can have on PMN rates. By 7 days, only 85.1% of known fills had occurred (575/676 = 85.1%), and by 14 days the number increases to 93.5%. Increasing the FW to 180 days would ensure that all known fills are classified as not being PMN; however, when considering the rationale behind measuring PMN, there must be some threshold after which the patient is not receiving the intended therapeutic benefit. Here, 30 days is a good candidate as 98.8% of known fills occurred by this time.

medication in the same therapeutic class[5,9] or a medication prescribed for the same indication.[24,25] Unlike non-specialty disease states such as hypertension or dyslipidemia, which have dominated PMN literature, most specialty disease states require the utilization of only one specialty medication at any given time. Some specialty diseases with multiple treatment options of comparable effectiveness (e.g., rheumatoid arthritis or inflammatory bowel disease), may have a higher rate of medication substitution between therapeutic classes from prescription to fulfillment based on insurer formulary requirements. Therefore, defining therapeutic equivalence as any specialty medication prescription written for the same treatment indication, rather than within a therapeutic class, should be sufficient for assessing the LBW and DW in specialty disease states. It may be assumed that using a broader definition of therapeutic equivalence such as any specialty oncology agent could produce lower PMN rates whereas using a narrow definition to include only a specific therapeutic class would result in higher PMN rates. Additionally, a broad definition of therapeutic equivalence limits the ability to assess a patient's ability to obtain the originally prescribed medication. For example, if therapeutic equivalence is defined as any specialty oncology agent, it would not be possible to assess the PMN rate for a first-in-class medication for patients previously on specialty oncology therapy. In this instance, and others, it may be appropriate to narrow the definition of therapeutic equivalence.

Call for clarification

The intent of this study was not to recommend one standard method of calculating PMN, as this has been previously purported for certain chronic conditions by PQA.[5] Rather, we aimed to describe the impact of varying common parameters used in the calculation on the PMN rates observed. Our findings illustrate that calculated PMN rates are altered based on parameter specifications. Therefore, we recommend that researchers clearly define, at minimum, the LBW, DW, and FW in their study methods. Similarly important, though not evaluated in our study, is reporting of: definition of therapeutic equivalence, source of prescribing and pharmacy fulfillment data, method of mapping prescription generation to fill data, and handling of transferred or cancelled prescriptions.

Limitations

This was a single-site study focused on self-administered oncology specialty medications. Results may not be generalizable to other disease states or chronic therapies. Additionally, most prescriptions generated from our health system were for white males and may not be representative of other populations. A more diverse population may increase variability in PMN rates, especially related to the FW as FW is directly linked to fill events which may be influenced by patients' socioeconomic behavior or status that may differ in diverse populations. However, as nearly all fill events (98.8%) occurred within 30 days of prescribing, our major findings would likely be robust even if more diverse populations would be included. Prescriptions sent outside the internal specialty pharmacy were excluded, limiting our understanding of non-health-system fills. Reasons for PMN were not assessed in this study. Scenarios that required a clinical or administrative change to the prescription that would result in a prescription that was not appropriate to be dispensed may have been included in the PMN assessment. We plan to use findings from this study for future research exploring the reasons for PMN in patients prescribed specialty medication.

Conclusions

PMN research is necessary to better understand the patient journey and barriers to treatment initiation, particularly within specialty pharmacy. Changing PMN calculation specifications can greatly impact results and their interpretation and application. Standardizing PMN methodology can help reduce variability and a thorough explanation of all elements of the PMN calculation should be reported in research involving PMN to accurately interpret findings.

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Credit author statement

Autumn Zuckerman: conceptualization, methodology, investigation, data curation, writing- original draft, writing- review and editing, supervision, project administration. Josh DeClercq: methodology, software, validation, formal analysis, data curation, writing- review and editing, visualization. Nisha Shah: conceptualization, methodology, investigation, data curation, writing- review and editing, supervision, project administration. Victoria Reynolds: investigation, data curation, writing- review and editing, supervision, project administration. Megan E. Peter: data curation, writing- review and editing, project administration. Aaron Pavlik: software, validation, data curation, writing- review and editing. Leena Choi: methodology, software, validation, formal analysis, data curation, writing- review and editing, visualization.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2021.03.016.

References

1. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43:521–530.
2. Dragomir A, Côté R, White M, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. *Value Health*. 2010;13:87–94.
3. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med*. 2006;166:1836–1841.
4. Penning-van Beest FJ, van der Bij S, Erkens JA, Kessabi S, Groot M, Herings RM. Effect of non-persistent use of oral glucose-lowering drugs on HbA1c goal attainment. *Curr Med Res Opin*. 2008;24:2523–2529.
5. Adams AJ, Stolpe SF. Defining and measuring primary medication nonadherence: development of a quality measure. *J Manag Care Spec Pharm*. 2016;22:516–523.
6. Lee SQ, Raamkumar AS, Li J, et al. Reasons for primary medication nonadherence: a systematic review and metric analysis. *J Manag Care Spec Pharm*. 2018;24:778–794.
7. Cocohoba J, Pohlman B, Tran JS, et al. Modeling specialty medicine access: understanding key health system processes and players. *J Am Pharmaceut Assoc*. 2003;59:43–50.e43, 2019.
8. Gadkari AS, McHorney CA. Medication nonfulfillment rates and reasons: narrative systematic review. *Curr Med Res Opin*. 2010;26:683–705.
9. Raebel MA, Carroll NM, Ellis JL, Schroeder EB, Bayliss EA. Importance of including early nonadherence in estimations of medication adherence. *Ann Pharmacother*. 2011;45:1053–1060.
10. Wang AA, Tapia C, Bhanji Y, et al. Barriers to receipt of novel oral oncolytics: a single-institution quality improvement investigation. *J Oncol Pharm Pract*. 2019, 1078155219841424.
11. Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Adv Ther*. 2011;28:51–61.
12. Tanaka Y, Kameda H, Saito K, et al. Effect of subcutaneous tocilizumab treatment on work/housework status in biologic-naïve rheumatoid arthritis patients using inverse

probability of treatment weighting: FIRST ACT-SC study. *Arthritis Res Ther*. 2018;20:151.
13. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. *Hepatology*. 2016;64:405–414.
14. Hanson RL. Specialty pharmacy and the medication access dilemma. *Am J Health Syst Pharm*. 2015;72:695.
15. Fischer MA, Choudhry NK, Brill G, et al. Trouble getting started: predictors of primary medication nonadherence. *Am J Med*. 2011;124:1081. e1089-1022.
16. Jackson TH, Bentley JP, David J, et al. Store and prescription characteristics associated with primary medication nonadherence. *J Manag Care Pharm*. 2014;20:824–832.
17. Liberman JN, Hutchins DS, Popiel RG, Patel MH, Jan SA, Berger JE. Determinants of primary nonadherence in asthma-controller and dyslipidemia pharmacotherapy. *Am J Pharm Benefits*. 2010;2:111–118.
18. Karter AJ, Parker MM, Moffet HH, Ahmed AT, Schmittdiel JA, Selby JV. New prescription medication gaps: a comprehensive measure of adherence to new prescriptions. *Health Serv Res*. 2009;44:1640–1661.
19. Fallis BA, Dhalla IA, Klemensberg J, Bell CM. Primary medication non-adherence after discharge from a general internal medicine service. *PLoS One*. 2013;8, e61735.
20. Thengilsdóttir G, Pottegård A, Linnet K, Halldórsson M, Almarsdóttir AB, Gardarsdóttir H. Do patients initiate therapy? Primary non-adherence to statins and antidepressants in Iceland. *Int J Clin Pract*. 2015;69:597–603.
21. Adamson AS, Suarez EA, Gorman AR. Association between method of prescribing and primary nonadherence to dermatologic medication in an urban hospital population. *JAMA Dermatol*. 2017;153:49–54.
22. Johnson TL, Parker AL. Rates of retrieval of self-injectable epinephrine prescriptions: a descriptive report. *Ann Allergy Asthma Immunol*. 2006;97:694–697.
23. Waalen J, Bruning AL, Peters MJ, Blau EM. A telephone-based intervention for increasing the use of osteoporosis medication: a randomized controlled trial. *Am J Manag Care*. 2009;15:e60–70.
24. Bauer AM, Schillinger D, Parker MM, et al. Health literacy and antidepressant medication adherence among adults with diabetes: the diabetes study of Northern California (DISTANCE). *J Gen Intern Med*. 2013;28:1181–1187.
25. Cheetham TC, Niu F, Green K, et al. Primary nonadherence to statin medications in a managed care organization. *J Manag Care Pharm*. 2013;19:367–373.