Medication Adherence Trajectories: A Systematic Literature Review

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ABSTRACT

BACKGROUND: Traditional adherence measures such as proportion of days covered (PDC) and medication possession ratio (MPR) are limited in their ability to explain patient medication adherence over time. Group-based trajectory modeling (GBTM) is a new methodological approach that visually describes the dynamics of long-term medication adherence and classifies adherence behavior into groups.

OBJECTIVES: To describe and compare trajectories of medication nonadherence reported in the medical literature, including identifying consistent trends in adherence trajectories and disease and patient characteristics that predict trajectory group membership.

METHODS: A systematic literature review was conducted in April 2020 in PubMed and CINAHL using MeSH terms and key words in appropriate combinations. Citations were screened for relevance using predefined inclusion and exclusion criteria and evaluated according to variables associated with group-based trajectory models.

RESULTS: 21 articles met the study criteria and were reviewed. Generally, studies identified 4 to 6 trajectory groups that described longitudinal medication adherence behavior. Most commonly identified trajectories were labeled as (a) consistent, high adherence, (b) declining adherence, (c) early and consistent nonadherence, and (d) initial nonadherence followed by an increase. Several predictors, including socioeconomic status, disease characteristics, and therapy initiation were routinely associated with group membership.

CONCLUSIONS: This review suggests that adherence trajectories and predictors of specific group membership may be similar across diverse disease states. GBTM describes longitudinal, dynamic patterns of medication adherence that may facilitate the development of targeted interventions to promote adherence. Implications for value-based payment systems are discussed in this review.

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What this study adds

- GBTM on oral medication adherence consistently identifies 4 to 6 similar medication adherence behavior trajectories irrespective of the disease state.
- Similar demographic and clinical characteristics have been shown to predict trajectory group membership across diverse disease states.
- This review concludes that GBTM may be a more appropriate approach to investigating and designing practice interventions for improving medication adherence.

Medication nonadherence is a major obstacle to improving health care outcomes in long-term therapies for chronic diseases.¹ It is associated with adverse health outcomes and higher health care costs.¹⁻³ Studies on medication adherence commonly use administrative claims data to quantify adherence with established metrics such as proportion of days covered (PDC) and medication possession ratio (MPR).⁴⁻⁶ These measures, which differ subtly in their calculations, summarize overall adherence with a single number based on the number of days a patient has medication on hand during a specified time period and assume that medication on hand is taken.

While PDC and MPR are well established in the literature and have garnered endorsements from organizations such as the Pharmacy Quality Alliance and the National Quality Forum,^{7,8} their limitations are also well documented.^{4,9} PDC and MPR measures can be insensitive to changes in patient behavior over time and circumstances.^{10,11} They are also most often used to classify patients dichotomously, with ratios above a specified threshold (e.g., PDC > 80%) denoting adherence,^{10,11} which may not adequately differentiate between clinically significant adherence behaviors. For example, a PDC of 79% is labeled nonadherent and a PDC of 81% is considered adherent, although the probability of therapeutic success is likely to be similar.

In reality, adherence to medication therapy is a dynamic process consisting of a series of stages of adherence and nonadherence over time during initiation, maintenance, and discontinuation phases of treatment.¹² This dynamic process is influenced by multiple factors related to socioeconomics, the health care system, diseases, treatments or regimens, and patients.^{1,13}

What is already known about this subject

- Static measures such as proportion of days covered or medication possession ratio may not adequately capture the fluid nature of medication-taking behavior and allow the identification of underlying factors that predict nonadherence behavior over a long period of time (e.g., over a period of 1 year).
- Group-based trajectory modeling (GBTM), which describes different medication adherence patterns as trajectories over time, has been increasingly used to investigate medication adherence patterns.

The fluid nature of medication-taking behavior and the underlying factors driving that behavior are not adequately captured with PDC and MPR ratios alone. Patient adherence may vary over time depending on an individual's employment status, family situation, new disease diagnosis, change in therapy, or any host of other factors. By quantifying adherence with a single ratio, PDC and MPR collapse a broad spectrum of adherence behaviors into a single number, thereby masking complex, dynamic, and longitudinal patterns of behavior.^{10,14} Indeed, a patient with a PDC of 60% may have been (a) highly adherent during the early stages of therapy but less adherent as time went on, (b) poorly adherent during the early stages of therapy but more adherent over time, or (c) intermittently adherent throughout the follow-up period.¹⁰ Each of these 3 patterns of taking medication would be classified as non-adherent using conventional measures and would be treated as a homogenous adherence group. Ignoring these underlying differences in the refill patterns and patients' adherence behavior may lead to missed opportunities to address barriers to appropriate medication use.

Group-based trajectory modeling (GBTM) is a method commonly used in the social sciences that elicits common trajectories, or progressions, of how a group of people behaves over a period of time. Lately, it has been used to evaluate adherence, overcoming the limitations of static measures such as annual PDC or MPR. Instead of providing a single adherence ratio, it describes different medication adherence patterns as trajectories over time.

With GBTM, patient administrative claims data are used to calculate monthly measures of adherence, which are then analyzed over time, clustering patients into similar patterns of longitudinal adherence behavior (e.g., always adherent or decreasingly adherent).¹⁰ The number of trajectory groups may be identified based on several criteria, including Bayesian information criteria, where a lower value indicates better fit,¹⁵ and Nagin's criteria for model adequacy,¹⁶ with consideration given to group size such that the proportion of patients in each group is not less than 5% of the total sample.^{15,17} Each method follows specific criteria to classify adherence groups based on their membership probabilities (highest likelihood probability to belong to certain groups). Once the final number of groups is selected, trajectories are plotted and presented in graphical form. Regression models may then be used to estimate and characterize the predictors of each trajectory.^{10,17}

Given the growing literature on GBTM medication adherence studies, there is a need to examine the commonalities and differences in models and the trajectories of adherence identified by them. If pharmacists, especially those within managed care organizations, can identify common different adherence trajectories and their underlying causes, they can develop population-based interventions to better address non-adherence. This systematic literature review describes studies

that used group-based trajectory models to identify common patterns of medication adherence. The review summarizes general characteristics of the studies concerning therapies chosen, populations examined, and study features.

Methods

Search Strategy

The literature review was conducted on April 2020 in PubMed and CINAHL databases using MeSH terms and key words in appropriate combinations and in accordance with PRISMA guidelines. Search terms were combinations of the following: (*group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory*) AND (*medication adherence OR "Medication Adherence"[Mesh]*), (*group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory*) AND (*fill prescription*), (*group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory*) AND (*medication compliance*), (*group based trajectory modeling OR group based trajectory models OR group based trajectory OR trajectory*) AND (*medication persistence*). To ensure complete capture of relevant articles, the authors conducted backward snowballing, by reviewing the references of the included articles.

Review Procedures and Study Selection

Titles and abstracts from search result articles were screened by 2 investigators based on inclusion and exclusion criteria. Disagreements pertaining to the inclusion and exclusion criteria were resolved by discussion with a third researcher. Studies that evaluated patient adherence to oral medications over time using group-based trajectory models and were published in English were included. Studies focusing on select special populations (i.e., children and pregnant women) were excluded because of the unique nature of medication-taking behaviors in these groups. Studies examining adherence to provider-administered biologics were excluded because adherence behavior may systematically differ from self-administered medications obtained from a pharmacy. Review articles, case reports, and prospective studies without results were also excluded.

Data Extraction

Two researchers extracted data regarding authorship, year of publication, country, population, type of treatment, sample size, number and shape of trajectory groups identified, clinical outcomes that were being assessed, and general conclusions that results from GBTM analysis.

Results

The search in PubMed and CINAHL yielded 248 articles. After screening for duplicates and applying inclusion and exclusion criteria, 20 research articles remained for analysis (Figure 1).

FIGURE 1 PRISMA Flowchart

GBTM=group-based trajectory modeling. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

After the full-text review, reference lists for included articles were searched, yielding 8 additional studies for inclusion.

All 28 papers were published in the last 10 years (2010–2020). Most studies were conducted in the United States ($n=17$, 60.7%),^{10,18–34} while the remaining were conducted in Europe ($n=7$, 25%),^{35–41} Taiwan ($n=1$, 3.6%),⁴² and Australia ($n=2$, 7.14%).^{43,44} Although a variety of medical conditions were explored in GBTM populations, the majority of studies focused on populations diagnosed with cardiovascular diseases ($n=19$, 67.9%).^{10,18,20,22–24,27,29,30,32–38,41,43,45} Study duration ranged from 9 months to 6 years,^{38,42} with most lasting 2 years or less ($n=22$, 78.6%). Table 1 summarizes the studies included in this review by the population characteristics, type of treatment, study duration, adherence measure, country, sample size, number of trajectory groups identified, and overview of the conclusions.

Number and Types of Trajectory Groups

In Table 1, the column “Trajectory Group” encompasses the number and general description of the adherence trajectories found in each of the included studies. The number of trajectory groups identified ranged from 3 to 7, although most studies ($n=18$, 85.7%) identified 4 to 6 trajectory groups. Regardless of the total number of trajectories identified, 19 studies identified the following 4 similar adherence trajectory groups: (1) consistent, high adherence, (2) declining adherence, (3) early and consistent nonadherence, and (4) initial nonadherence followed by a slight increase in adherence.

Consistent, High Adherence. All of the published studies identified a “perfect adherence” or “nearly perfect adherence” trajectory composed of patients who consistently registered a monthly probability of PDC or MPR over 80% for the duration of the study. In most studies, ($n=22$, 78.6%), the consistent, high adherence trajectory group comprised the largest proportion of patients, ranging from 21% to 80% of patients in the study. More specifically, 14 studies observed a consistently adherent group that represented more than 40% of the sample.^{18–20,22–26,29,32,33,35–38,42–45}

Declining Adherence. Studies that identified more than 1 declining adherence trajectory varied primarily in the shape and speed of decline. The most commonly identified declining adherence trajectory ($n=26$, 92.9%) was one characterized by a gradual decline in adherence, with “falling” adherence rates starting anywhere between the third and ninth month.^{10,19,20,22–24,26–28,30,37–39,42,43,46} Studies also often identified a rapid trajectory ($n=22$, 78.6%), in which adherence immediately declines within the first 2 months of therapy initiation.^{10,19,20,22–24,26–28,30,33,37,39,40,43–46}

Early and Consistent Nonadherence. All articles reported early nonadherent behaviors. In these trajectory groups, adherence steeply declined well below 80% after the first months. In some studies ($n=4$, 14.3%), this group was designated as rapid decline in adherence, or persistent nonadherers.^{20,23,43,46} In all studies, the steep decline in adherence was usually followed by a consistently very low adherence throughout the study duration. However, adherence analyses based on administrative claims data require at least 1 fill of the prescribed medicine. Notably, adherence measures using administrative claims data do not capture patients with primary nonadherence who never pick up their initial fill. Group-based trajectory models using claims data can only identify patients with secondary nonadherence and may therefore underestimate the true proportion of consistently nonadherent patients, which would more accurately include patients with primary and secondary nonadherence.

Initial Nonadherence Followed by an Increase. The fourth commonly identified trajectory group described patients whose

TABLE 1 Summary of Identified Studies

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
Dillon et al., 2019 ³⁶	1. Classify adherence to antihypertensives using PDC and GBTM 2. Evaluate the longitudinal association between community pharmacy antihypertensive refill adherence metrics (GBTM and PDC) and the number of hospital visits and GP visits	Patients aged ≥ 65 years	Multiple classes of antihypertensives	1 year	Republic of Ireland	905	PDC	1. Perfect adherence 2. High adherence 3. Low adherence	Hospital visit, GP visit	PDC could be used to rank patients by adherence level and be combined with other adherence measurements, such as individual adherence trajectory graphs, to provide a richer picture of patient adherence behavior
Marcum et al., 2019 ¹⁸	1. Examine antihypertensive and statin adherence 2. Compare people who went on to develop dementia with those who did not	Patients aged ≥ 65 years	Multiple classes of antihypertensives and statins	3 years	United States	4,368	PDC	1. Perfect adherence 2. Moderate nonadherence 3. Slow decline 4. Rapid decline	–	Patterns of medication adherence may be useful to identify a subset of people at higher likelihood of developing dementia
Winn et al., 2019 ¹⁹	1. Examine how adherence to ET for women with breast cancer was impacted by reducing copayments for ETs by the introduction of generic ETs among women who do not receive a subsidy compared with those that do receive a subsidy and are not exposed to any changes in copayments by using GBTM	Women with breast cancer aged > 66 years	ET	1 year	United States	3,344	PDC	1. Perfect adherence 2. Slow decline then increase 3. Rapid decline, then increase 4. Slow decline 5. Rapid decline 6. Low adherence	–	Describes a new approach to identify heterogeneous effects when using an interrupted time series research design
MacEwan et al., 2018 ²⁰	1. Identify patients' antipsychotic adherence patterns 2. Assess whether antipsychotic adherence patterns can predict other medications adherence patterns	Patients with serious mental illness who initiated an atypical antipsychotic and were also taking an SSRI, biguanide, or an ACE inhibitor	Atypical antipsychotic, SSRI, biguanides, and ACE inhibitors	1 year	United States	431,591	PDC	1. Perfect adherence 2. Rapid decline, then increase 3. Slow decline 4. Rapid decline	Adherence patterns for SSRIs, biguanides, and ACE inhibitors	Among patients with multiple chronic mental and physical illnesses, patterns of atypical antipsychotic adherence were useful predictors of adherence patterns to a patient's adherence to ACE inhibitors, biguanides, and SSRIs

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TABLE 1 Summary of Identified Studies (continued)

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
Feldman et al., 2018 ⁴⁶	1. Identify adherence trajectories for patients taking HCQ 2. Identify predictors of nonadherence to HCQ	Adult Medicaid patients with systemic lupus erythematosus	HCQ	1 year	United States	10,406	PDC	1. Perfect adherence 2. Moderate nonadherence 3. Low decline 4. Very rapid decline	–	HCQ adherence is a dynamic behavior that declines over the first year of use
Franklin et al., 2018 ²²	1. Identify adherence trajectories for statins, antihypertensives, and oral antidiabetics 2. Identify predictors of nonadherence trajectories 3. Evaluate the accuracy of predictions of medication adherence based on EHR data versus claims	Tufts Health Plan Medicare Advantage beneficiaries aged 65 and older, receiving care at Harvard Vanguard Medical Associates	Statins, multiple classes of antihypertensives, and oral antidiabetics	1 year	United States	11,479	PDC	1. Perfect adherence 2. Decline after 9 months 3. Moderate nonadherence 4. Decline after 6 months 5. Rapid decline	–	EHR data can provide good predictions of adherence trajectory
Schaffer et al., 2017 ⁴³	1. Compare statin adherence in individuals initiating combined amlodipine/atorvastatin therapy as FDC or free combination 2. Identified subgroups benefiting most from FDCs 3. Identified predictors of adherence trajectories	All patients initiating amlodipine in combination with atorvastatin, either as FDC or in free combination	Amlodipine and atorvastatin as FDC and free combination	2 years	Australia	3,996 (FDC), 5,434 (free combination)	PDC	1. Perfect adherence 2. Moderate adherence 3. Slow decline 4. Very rapid decline	–	The amlodipine/atorvastatin FDC was associated with greater statin adherence among prevalent statin users
Dillon et al., 2018 ³⁵	1. Characterize adherence to antihypertensive medication 2. Test predictive validity of GBTM in BP measurement	Patients aged ≥ 65 years	Multiple classes of antihypertensives and statins	1 year	Republic of Ireland	905	PDC	1. Perfect adherence 2. High adherence 3. Moderate nonadherence	–	GBTM identified 3 trajectories; however, did not show predictive validity with BP measurement
Hargrove et al., 2017 ²³	1. Use GBTM to identify antihypertensive adherence trajectories 2. Compare adherence trajectories to traditional adherence measures 3. Identify patients characteristics associated with adherence trajectories	Medicare patients aged ≥ 65 years	Multiple classes of antihypertensives and statins	1 year	United States	282,520	PDC: used to compare identifying adherent and non-adherent months	1. Perfect adherence 2. Rapid decline, then increase 3. Moderate decline, then increase 4. Moderate decline 5. Rapid decline 6. Very rapid decline	–	GBTM is an effective method to identify patterns of medication adherence compared with PDC

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TABLE 1 Summary of Identified Studies (continued)

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
MacEwan et al., 2016 ²⁴	1. Identify adherence trajectory for oral atypical antipsychotics 2. Identify associated factors	Adult schizophrenia patients	Oral atypical antipsychotic	1 year	United States	29,607	PDC	1. Perfect adherence 2. Decline after 3 months 3. Decline after 6 months 4. Decline after 9 months 5. Rapid decline, then increase after 6 months 6. Very rapid decline	Psychiatric inpatient admission and ED visit	Adherence patterns identified by GBTM are more varied than research based on PDC; lower adherence trajectories associated with higher ED visits
Aarnio et al., 2016 ³⁷	1. Identify adherence trajectories of statin 2. Examine association between SEP and adherence trajectories	Patients aged 45-75 years	Statin	18 months	Finland	116,846	PDC: used to compare predictors ability to identify nonadherent participants	1. Perfect adherence 2. High adherence 3. Rapid decline, then increase 4. Moderate decline 5. Rapid decline 6. Very rapid decline	–	SEP is associated with low adherence groups; overall, GBTM provides insight to dynamics of adherence behavior
Librero et al., 2016 ³⁸	1. Identify adherence trajectories for ACEI, statin, beta blocker, and antiplatelet 2. Identify associated factors	Patients discharged with CHD	ACEI/ARB, beta blockers, statins, and antiplatelet	9 months	Spain	7,462	PDC	1. Perfect adherence 2. Low adherence, then increase 3. Moderate decline, then increase 4. Moderate decline 5. Rapid decline	–	GBTM identified distinct adherence trajectories for differences in preventive medication for CHD; it showed advantage over traditional measures
Mårdby et al., 2016 ³⁹	1. Identify adherence trajectories of antidepressants 2. Identify associated factors	Patients aged 18-85 years	Citalopram	24 months	Sweden	54,248	MPR	1. Perfect adherence 2. Moderate decline 3. Rapid decline, then increase 4. Rapid decline 5. Very rapid decline	–	1. GBTM identified 5 distinct patterns 2. Low adherence trajectories associated with lower SEP

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TABLE 1 Summary of Identified Studies (continued)

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
Lo-Ciganic et al., 2016 ²⁵	1. Identify adherence trajectories of oral hypoglycemic and associated factors 2. Examine association with clinical events	Patients aged 18-64 years with DM	Oral hypoglycemic medication	1 year	United States	16,256	PDC: used to compare GBTM in the ability to predict outcome	1. Perfect adherence 2. High adherence 3. Moderate decline 4. Moderate nonadherence 5. Rapid decline, then increase 6. Rapid decline 7. Very rapid decline	1. DM related ED visit/hospitalization 2. All cause ED visit/hospitalization	Lower adherence trajectories associated with higher ED/hospitalization events
Winn et al., 2016 ²⁶	1. Identify adherence trajectories of ET 2. Identify associated factors 3. Examine association with mortality	Women with breast cancer	ET	1 year	United States	9,492	PDC: used to compare GBTM in the ability to predict outcome	1. Perfect adherence 2. Slow decline 3. Rapid decline, then increase 4. Moderate decline 5. Rapid decline	All-cause mortality	Low adherence groups associated with higher mortality rate
Chen et al., 2016 ⁴²	1. Identify adherence trajectories of hypoglycemic 2. Identify associated factors	Patients aged ≥ 18 years type 2 diabetes	Oral hypoglycemic medication	6 years	Taiwan	12,123	MPR	1. Perfect adherence 2. Moderate adherence, then increase 3. Moderate decline 4. Low adherence, then increase	—	GBTM help in identifying heterogeneity of medication adherence
Franklin et al., 2015 ²⁷	Identify adherence trajectories of statin	Patients aged ≥ 65 years	Statins	1 year	United States	77,703	PDC	1. Perfect adherence 2. Moderate adherence 3. Rapid decline, then increase 4. Moderate decline, then increase 5. Rapid decline 6. Very rapid decline	—	Initial adherence behavior associated with better future adherence

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TABLE 1 Summary of Identified Studies (continued)

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
Newman-Casey et al., 2015 ²⁸	1. Identify adherence trajectories of glaucoma medication 2. Identify associated factors	Patients aged ≥ 40 years treated for glaucoma	Glaucoma medication	4 years	United States	1,234	MPR	1. Perfect adherence 2. Moderate nonadherence 3. Moderate decline 4. Low adherence, then increase 5. Rapid decline	–	Adherence patterns for first year, had great impact on future adherence behavior
Juarez et al., 2015 ²⁹	1. Identify adherence trajectories of ACEI 2. Identify associated factors	Patients with CHF	ACEI	6 years	United States	10,986	MPR	1. Perfect adherence 2. Moderate decline 3. Low adherence, then increase 4. Rapid decline	–	Patient factors associated with low adherence trajectories can be used to target interventions
Franklin et al., 2015 ³⁰	1. Identify adherence trajectories of statin 2. Examine association with clinical events	Patients in the UnitedHealth Optum Research Datamart, aged 35-64 years	Statins	1 year	United States	519,842	PDC: used cross-validation methods to ascertain if initial PDC could predict trajectory membership	1. Perfect adherence 2. Rapid decline then increase 3. Moderate decline 4. Moderate decline, then increase 5. Rapid decline 6. Very rapid decline	Hospitalization for an acute coronary event, revascularization, cerebrovascular event, or heart failure	Adherence trajectories predicts future clinical outcomes better than PDC
Franklin et al., 2013 ¹⁰	1. Identify adherence trajectories of statin 2. Identify associated factors	Patients initiating a statin in CVS Caremark	Statins	15 months	United States	264,789	PDC	1. Perfect adherence 2. Rapid decline then increase 3. Moderate decline 4. Moderate nonadherence 5. Rapid decline 6. Very rapid decline	–	GBTM summarized adherence patterns better than traditional measures
Vadhariya et al., 2019 ³³	1. Identify distinct trajectories of adherence to statin therapy 2. Identify sociodemographic and clinical predictors of trajectory membership	Patients enrolled in a Medicare Advantage Plan	Statins	12 months	United States	7,850	PDC	1. High/nearly perfect adherence 2. Declining adherence, then increase 3. Gradual decline 4. Rapid decline	–	Adherence trajectories are consistent with previous findings in the literature; patient characteristics are found to be predictors of trajectory membership

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TABLE 1 Summary of Identified Studies (continued)

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
Lambert-Cote, et al. 2020 ⁴⁰	1. Identify adherence trajectories and characterize trajectory shapes 2. Identify factors associated with group membership	Women with breast cancer living in metropolitan areas covered by National Health Insurance plan	Adjuvant endocrine therapy	5 years	France	674	PDC	1. Very high adherence 2. High adherence 3. Slow decline 4. Moderate decline 5. Quick decline	–	Previous exposure to chemotherapy and personalized care plan were found to be predictors of trajectory membership; dynamic behavior of adherence not fully captured by traditional annualization of PDC
Ajrouche et al., 2020 ⁴¹	1. Identify adherence trajectories of low-dose aspirin 2. Describe trajectories based on primary or secondary indication for low-dose aspirin 3. Identify predictors of low-dose aspirin adherence trajectory membership	Patients with at least 3 months of follow-up after first low-dose aspirin delivery	Low-dose aspirin	3 years	France	11,793	PDC	1. Perfect adherence 2. Declining adherence 3. Declining adherence then increase 4. Low adherence	Hemorrhagic events	GBTM provides a better understanding of longitudinal trends by yielding visual developmental trajectories; nonadherence trajectories seem to be associated with uncertain efficacy of using low-dose aspirin in primary prevention
Hickson et al., 2020 ³²	Identify number of adherence trajectories in statin users in the 6 months before an acute myocardial infarction.	Medicare beneficiaries	Statins	6 months	United States	113,296	PDC	1. Persistently adherent 2. Moderately adherent 3. Declining adherence 4. Persistently nonadherent	–	GBTM comprises subjective decisions to assess longitudinal trends in adherence behavior; including spaghetti plots to confirm the adequacy of trajectory group membership may improve internal validity
Zongo et al., 2019 ⁴⁵	Identify number of adherence trajectories before and after acute coronary syndrome or stroke.	Patients hospitalized for acute coronary syndrome	Lipid-lowering drugs	2 years (1 year before and 1 year after)	Canada	10,623	PDC	1. Nearly perfect adherence 2. Gradual decline 3. Moderate adherence then gradual increase 4. Rapid decline 5. Poor adherence throughout	–	The occurrence of acute coronary syndrome or stroke seems to influence continued behavior of adherence

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TABLE 1 Summary of Identified Studies (continued)

Authors	Objectives	Population	Type of Treatment	Length of Study Period	Country	Sample Size	Adherence Measure	Trajectory Group	Clinical Outcomes	Conclusions
Hernandez et al., 2019 ³⁴	Identify number of adherence trajectories of patients about to initiate oral anticoagulants for atrial fibrillation	Patients diagnosed with atrial fibrillation	Oral anti-coagulants	12 months	United States	34,898	PDC	1. Perfect adherence 2. Gradual decline 3. Initial low adherence then increase 4. Consistently poor adherence	–	Patients at higher risk of bleeding or stroke are more likely to go through poorer adherence trajectories; late initiators are also more likely to belong to nonadherence trajectories
Tervonen et al., 2019 ⁴⁴	Identify adherence trajectories and treatment and patient characteristics associated with discontinuation and restart of therapy.	Women diagnosed with HER-2 positive breast cancer	ET	5 years	Australia	2,656	MPR	1. Perfect adherence 2. Stable with late decline 3. Moderate decline 4. Quick decline then stable 5. Quick decline	Discontinuation and restart of therapy	Consistent trajectories were found; GBTM analysis allows the identification of critical time points that may warrant intervention: 6 months, 1.5 years, and 4 years after initiation

ACE=angiotensin-converting enzyme; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blockers; BP=blood pressure; CHD=coronary heart disease; CHF=congestive heart failure; DM=diabetes mellitus; ED=emergency department; EHR=electronic health record; ET=endocrine therapy; FDC=fixed dose combination; GBTM=group-based trajectory modeling; GP=general practitioner; HCQ=hydroxychloroquine; MPR=medication possession ratio; PDC=proportion of days covered; SEP=socioeconomic position; SSRI=selective serotonin reuptake inhibitor.

adherence was poor at the beginning of the study period but would gradually improve over time ($n=18$, 64.3%).^{10,19,20,23-30,33,37-39,41,42,45} This rebound in adherence was more frequent following a period of rapid declining adherence ($n=12$, 42.9%), although 5 studies identified trajectories with improving medication adherence following rapid and gradual declines.^{19,23,27,30,34} This trajectory was different from the others that appeared to display an initial pattern of nonadherence, which evolved to a pattern of increasing adherence. Despite not being referenced in the included studies, since most used data from administrative claims, this transition may be indicative of some event or intervention that explains the change in the adherence patterns of patients.

In studies with a follow-up period between 9 and 18 months, there was a clear pattern in the time point at which an increase would be observable in the declining adherence trajectory (4-6 months).^{10,20,23-27,30,33,34,37,38,45} The studies with longer follow-up periods (3-6 years) described increases at different time points, primary between the first and second year.^{26,40,41,44} The type of drug being analyzed also varied, including statins, antipsychotics, antidepressants, and angiotensin-converting enzyme inhibitors, which does not indicate a common underlying

reason for the increase in adherence after a period of declining adherence.^{28,41,42,44} In a study with a follow-up period of 5 years, a declining adherence trajectory increased to a stable level of adherence, suggesting that a trend of reaching a plateau in adherence may be observed if follow-up periods were extended beyond 18 months.⁴⁴ It is possible that the trend of reaching a plateau in adherence would be observed in the shorter follow-up period studies.

Drug Classes Studied

With the exception of 1 study,³⁸ all studies focused on adherence to a single drug class over time. Single drug class studies examined trajectories of a wide selection of medications: antihypertensives, statins, oral antihyperglycemic drugs, antipsychotics, antidepressants, treatment for systemic lupus erythematosus, glaucoma, and endocrine therapy (Table 1).

Four of the 6 studies that focused exclusively on statin adherence identified 6 adherence trajectories, while the other 2 found only 4 trajectories. Studies that examined statins and antihypertensives, however, varied in the number of identified trajectories (3-6 trajectories), as did studies that included oral antidiabetic agents (4-7 trajectories).

Patient Characteristics Associated with Trajectories

Patient sociodemographic and clinical characteristics were commonly associated with the likelihood of belonging to specific adherence trajectories in the included studies. Juarez et al. (2015) found that race, (e.g., black, Asian, and Pacific Islanders) was associated with belonging to nonadherence trajectories when compared with white patients.²⁹ The same types of associations were found in other studies in which individuals who were younger, nonwhite, males, with more severe disease and comorbidities, and with lower educational attainment and socioeconomic status were more likely to follow low adherence trajectories.^{10,25,26,28,29,33,39,42,46}

Conflicting results were found in 2 studies, in which females were more likely to belong to nonadherence trajectories.^{33,41} Low adherence trajectories were found for patients from a lower socioeconomic status^{1,30,32} and for individuals with more severe diseases and comorbidities.^{24,46} Treatment complexity, race, previous history of the disease, frailty, concomitant use of opioids, and comorbidities were also associated with lower or nonadherence trajectories.^{22-26,28,35,37-39,46} Adherence trajectories were influenced by the experiences that patients had with taking other medications. MacEwan et al. (2018) found that adherence to atypical antipsychotic drugs can be a predictor of adherence to other medications.²⁰ Previous medication use was also found to be a predictor of higher adherence in other studies.^{23,35,43}

Patients in groups defined by declining adherence followed by an increase seem to have particular features. Although most studies found typical sociodemographic characteristics in patients in nonadherence trajectories, drug abuse, alcoholism,²⁴ hypertension,²³ a higher number of comorbid diagnoses,³⁸ and higher levels of out-of-pocket expenditures³⁸ were each reported to be overrepresented in declining adherence or nonadherence trajectories. In contrast, other characteristics seemed to have made patients less likely to belong to declining adherence trajectories or declining adherence followed by increasing trajectories. These characteristics included higher adherence to previous medication and being female outside of the labor market.^{20,37}

Finally, the only study with a pre/post approach found that patients who were previously in a declining followed by increase in adherence trajectory were more likely to belong to nearly perfect adherence trajectories after a critical medical event (i.e., acute coronary syndrome).⁴¹

Trajectories and Health Care Resource Utilization and Health Outcomes

Five studies examined and found a relationship between adherence trajectories and health care events (e.g., hospitalization events, emergency department [ED] visits, adverse events, or death),^{24-26,30,36} reporting that consistent, high adherence trajectories were associated with lower health care resource

utilization and improved health outcomes. Specifically, fewer hospitalizations were seen among patients in consistent, high adherence trajectories for antihypertensives,³⁶ statins,³⁰ and oral antidiabetic drugs,²⁵ with similar trends for reductions in ED visits in studies on antipsychotics and oral antidiabetics.^{24,25} More use of health care resources was not always associated with belonging to poor adherence trajectories. Although not specific to increased health care resource utilization, a more individualized approach to treatment plans seemed to improve the outlook of medication adherence. In Lambert-Côté et al. (2020), women with breast cancer who had received a personalized treatment plan that comprised receiving a written document with information and resources available throughout the treatment duration provided at diagnosis were more likely to belong to consistent, high adherence trajectories.⁴⁰

Conversely, patients in consistently nonadherent or declining adherence trajectories had a significantly increased risk of adverse outcomes. Patients on endocrine therapy in the rapidly and slowly declining adherence trajectories had a significantly higher risk of death compared with those in perfect adherence trajectories.¹⁹ Consistent nonadherence trajectory group membership was associated with a higher risk of cardiovascular events (e.g., hospitalization for acute coronary event, revascularization, cerebrovascular event, or heart failure) in patients taking statins.³⁰

Predictive Validity of GBTM

Five studies compared GBTM with conventional dichotomous measures (e.g., PDC), and all concluded that GBTM is advantageous, namely, because of the ability to encapsulate the trends of medication adherence over a period of time.^{23,25,26,30,37} Of these, 3 studies used multinomial logistic regression and computed the c-statistic to compare predictive validity of using GBTM versus dichotomized periodic PDC.^{23,25,26} However, the comparison in each study focused on different aspects. Hargrove et al. (2017) reported that a 6-group trajectory model better distinguished between adherent and nonadherent months than either PDC or even proportion of months covered (another possession-based adherence measure).²³ Lo-Ciganic et al. (2016) reported the c-statistic to compare dichotomized PDC and group-based trajectory models in predicting diabetes-related hospitalization and ED visits.²⁵ In Franklin et al. (2015), the c-statistic was used to compare the group-based trajectory model and dichotomized PDC in predicting cardiovascular events. In all situations, the c-statistic of GBTM fared better than the traditional dichotomized PDC $\geq 80\%$ threshold approach.³⁰ While the other 2 studies did not use multinomial logistic regression to compare GBTM to the traditional PDC $> 80\%$ approach, the respective authors argued that GBTM provided a more refined approach in identifying longitudinal trends. Aarnio et al. (2016) found GBTM to be comparable with PDC in identifying relationships between nonadherence and

FIGURE 2 Illustration of Similar Medication Adherence Trajectories

lower socioeconomic status, but that GBTM provided a more differentiating approach to analyzing nonadherent groups.³⁷ Winn et al. (2016) also determined that GBTM better differentiated adherence groups.²⁶

Discussion

GBTM has gained traction in adherence research based on its ability to better capture the temporal and fluid patterns of medication adherence compared with static, conventional measures. This review found that 4 to 6 trajectory groups could be used in most cases to describe medication-taking behavior over time. The most commonly identified trajectories can be described using the following labels: (a) consistent, high adherence, (b) declining adherence, (c) consistent nonadherence, and (d) initial nonadherence followed by an increase. Studies that identified fewer or more trajectories than 4 to 6 may have been affected by high adherence of patients studied, bias in selecting study subjects, the nature of the drugs studied, unique characteristics of patient populations, and differences in the rate of decline from adherence to nonadherence.^{25,36} Figure 2 shows the general trend identified in this literature review. Generally, adherence trajectories can be summarized by 4 trajectory groups, with the declining adherence trajectory possibly occurring at different rates (fast and slow).

The value provided by GBTM over current measures such as PDC and MPR is that it describes behavior over time instead of at discrete time periods. Understanding the temporal changes in behavior is important in evaluating and predicting influences on patient adherence. Hypothetically, a patient who interrupts medication taking because of complications might have a different trajectory than the patient who stops because of an issue of affordability or other complication, assuming that affordability and complications happen at different time points. Rather than classifying patients into dichotomous adherent and nonadherent groups, GBTM provides the longitudinal perspective to understand and describe patterns of nonadherence.

The distillation of adherence trajectories has the power to differentiate between underlying causes of nonadherence in a way that periodic dichotomization of PDC cannot. Early nonadherence can be a result of adverse events that otherwise would not be identified if the patient did not follow-up with a health care professional.^{20,23,43,46} Similarly, declining adherence followed by an increase, may be related to specific medical events that resulted in increased motivation to resume the treatment plan, suggesting that targeted interventions following medical events may be effective in improving adherence in these patients.⁴¹ These patterns should be explored through further research into the causes and potential solutions to nonadherence trajectory groups.

When contrasted with dichotomous PDC and MPR measures, GBTM offers a richer description of patient behavior. In Mårdby et al. (2016), the simple dichotomized PDC analysis showed that 50% of the patient population was nonadherent.³⁹ However, when a GBTM analysis was conducted, they found that a significant portion of the patients initially classified as nonadherent actually belonged to group with declining adherence that later increased. The finding of a subgroup with GBTM suggests heterogeneity among nonadherents that requires a more sophisticated array of interventions to improve medication adherence.

Other implications result from this review. Payers such as the Centers for Medicare & Medicaid Services and other private health insurers provide discounts and rebates for providers who meet certain quality measures, such as medication adherence. Specifically, Medicare Part D plans incorporate medication adherence as a significant component of their quality-based payment program (Medicare star ratings).^{47,48} In 1 study, 2 trajectories (declining followed by an increase and slow decline) were found to have no difference in risk of mortality when compared with the consistent, high adherence trajectory.²⁶ Therefore, it is likely that further research may elicit other optimal thresholds of adherence. Thus, systems that either reward or penalize providers based on medication adherence measures should use methods that appropriately demonstrate variations in medication adherence.

Moreover, GBTM has already served to develop a tailored motivational interviewing system based on adherence trajectories. The individualization of interventions not only allows for a better use of available resources but is able to produce significant improvements in adherence.⁴⁹ Likewise, using GBTM may also allow the identification of patients who are keen on following a specific adherence trajectory and, consequently, develop an action plan to invert the trend. Future research should clarify significant thresholds of medication adherence improvements that result in improvement of patient outcomes, as opposed to computing an average medication adherence percentage in a given period.

Limitations

Some limitations were identified in the studies in this review. It was apparent that some of the studies used different criteria to fit the final models. For example, despite the criteria for model fit, 1 study forced models ranging from 1 to 4 trajectory groups.⁴² This lack of consistency of the criteria used in the GBTM method can skew the overall conclusion of how many adherence groups exist in the general population.

Another limitation lies in the measures used to calculate GBTM, which is typically PDC. Adherence using PDC is assessed through pharmacy-paid claim data. Prescription fill records only indicate that a patient received the medication but does not indicate if the medication was taken as directed. In addition, PDC does not measure primary medication adherence, which happens when newly prescribed medications are never obtained by the patient. Therefore, analyzing adherence using pharmacy-paid claims data does not display patients who never really fill their prescriptions.

Finally, study heterogeneity could introduce bias in this review. Studies varied by their length of time (12 months to 24 months), number and types of medicines examined, practice setting, patient population, and more. Any of these variables can bias study outcomes in a way that masks meaningful results.

Conclusions

The findings of this review provide a summary of the evidence about patterns of medication adherence, and they show consistency with what is currently known. In most studies, a consistently adherent trajectory group was found, which typically made up a significant portion of the study sample. While previous literature reports that 50% of patients are typically adherent with their medications,^{1,13} it is clear that using a GBTM approach provides a richer perspective of patient adherence behavior. Adherence in patient populations in this study also found demographic and other variables associated with adherence found in the literature. Low adherence trajectories were commonly associated with low socioeconomic status, being nonwhite, and low health care utilization.

As more is learned about the number, shape, and causes of trajectories, future research will need to be conducted to identify how health care interventions can influence nonadherence trajectories. Interventions may need to be timed differently for different stages of adherence trajectories. The acuity of care given might also need to vary across different trajectories depending on patient needs or circumstances.

Public policy might also be informed by a better understanding of patient behavior over time. Public and private payers of prescription medications may need to adjust incentives linked to adherence measures. For instance, the CMS Star Ratings Program associated with Medicare Part D insurance plans use medication adherence as a significant component of the quality-based payment program.^{47,48} As shown in this review, it is possible that clinical outcomes (e.g., mortality) are not significantly different between perfect adherence trajectories and other trajectories currently classified as nonadherent (PDC < 80%). We conclude that adherence measurement by dichotomization of period PDC alone might lead to unintended consequences or missed opportunities. Future research into this topic is needed to better understand how GBTM can be used to improve medication adherence interventions.

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DISCLOSURES

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