Accuracy of Prescription Claims Data in Identifying Truly Nonadherent Patients

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ABSTRACT

BACKGROUND: Administrative claims data are increasingly used to identify nonadherent patients. This necessitates a comprehensive review and assessment of their accuracy in identifying nonadherent patients.

OBJECTIVES: To (a) compare administrative claims-based measures of adherence with nonadherence verified by patient interview; (b) determine if and to what extent patients classified as nonadherent based on prescription claims differ from patients classified as nonadherent based on interventions designed to gather multiple types of medication lists to compare against the prescription fill history; and (c) assess the various patient-reported reasons for nonadherence.

METHODS: A cross-sectional study was used to identify patients from the Southern Piedmont Community Care Network of North Carolina who were enrolled with Medicaid between January 1, 2012, and May 31, 2013, and were using prescription medications for 1 or more chronic conditions. Patients with more than a 30-day gap in refill history were identified using prescription claims and were interviewed by pharmacists to assess the reasons for nonadherence. Based on the patient-reported reasons for a gap in refill, patients were classified as interview-verified nonadherent patients or interview-verified adherent patients. The positive predictive value of prescription claims in identifying nonadherent patients was calculated, and descriptive statistics were reported. Characteristics of interview-verified nonadherent patients were compared with adherent patients using t-tests and chi-square statistics.

RESULTS: 1,425 patients representing 2,936 patient-class of medication combinations were included in the final analysis. 824 (28.07%) of the 2,936 records that were flagged as nonadherent using claims analysis were confirmed as adherent during patient interviews. The positive predictive value of claims records in identifying nonadherent patients was 0.72. The 2 most common reasons for patients to be misclassified as nonadherent in claims data following self-report were discontinuation of medication on prescribers' directions (21.93%) and having an alternate channel for receiving the medication (6.13%). Among interview-verified nonadherent patients, side effects, patient beliefs, education, and socioeconomic barriers were the most common patient-reported reasons for gaps in refill.

CONCLUSIONS: Prescription claims may underestimate adherence in patients. When interviewed directly by a pharmacist, most patients reported discontinuation of medication as per prescribers' directions. To determine the overall validity of prescription claims data, further analysis is required to assess its accuracy in identifying truly nonadherent patients among those who are identified as nonadherent by claims data.

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What is already known about this subject

- Various measures of adherence, such as proportion of days covered and gap analysis, in prescription claims data are commonly used to identify nonadherent patients
- Existing estimates of medication nonadherence using prescription claims data are of limited use if their accuracy cannot be established.

What this study adds

- This study compares claims-based measures of adherence with adherence verified by patient interview.
- This study enlists the barriers to filling prescriptions as cited by nonadherent beneficiaries in a Medicaid program.
- Through patient interviews, this study shows that claims-based data may misidentify medication nonadherence among patients appropriately discontinuing or changing treatment and in patients obtaining medications from alternative sources.

Medication nonadherence is generally low in common chronic conditions.¹⁻³ On average, 20%-50% of patients are not adherent to their medical therapy.^{4,5} Suboptimal treatment can lead to worsened clinical outcomes, increased use of medical resources, and higher health care costs.⁶⁻⁹ Medication nonadherence appears to be an even more complex challenge among patients in the Medicaid population, in which many have disabilities, multiple chronic conditions, and low health literacy levels.^{10,11}

To improve patient medication adherence and overall patient outcomes, care team concepts have gained more popularity in recent years.¹²⁻¹⁵ To ensure efficiency and success of such programs, it is important to identify target intervention groups such as high-risk, high-cost individuals with a variety of chronic medical conditions. Identifying nonadherent patients is often the first challenge in targeting groups that will benefit the most from such interventions. Automated pharmacy dispensing databases from a variety of sources, such as government insurance claims and managed care organization prescription claims, are increasingly being used to identify patients who are nonadherent to their therapy. Agencies such as the National Quality Forum have endorsed medication adherence, specifically proportion of days covered (PDC),

FIGURE 1 Self-Reported Reasons of Nonadherence

PDC = proportion of days covered.

as an indicator of quality in drug therapy management. The increasing use of prescription claims to measure adherence necessitates a comprehensive review and validation of their use. Previous studies that have looked at accuracy of prescription claims data in estimating adherence have focused on the completeness of pharmacy claims data.¹⁶⁻¹⁸

To our knowledge, no previous research has evaluated the effect of change in prescribers' directions for medication use on adherence measured through pharmacy claims data. We designed this retrospective observational study of a pharmacist-led intervention originally designed to review medication profiles and provide comprehensive medication reviews for drug therapy problem discovery in order to help understand the characteristics of patient groups that are likely to be identified as nonadherent through analysis of health care records. The primary objective of our study was to compare administrative claims-based nonadherence to nonadherence verified by patient interview. Our secondary objective was to determine if and to what extent patients classified as nonadherent based on prescription claims differ from patients classified as nonadherent based on pharmacist-initiated interviews. Furthermore, the study also sought to assess the various patient-reported reasons for nonadherence.

Methods

Study Design

This study used a cross-sectional study design that included a sample of North Carolina Medicaid patients with prescription drug benefits and using Community Care of Southern Piedmont's (CCSP) care management and pharmacist intervention services.

Study Population

In North Carolina, a patient-centered team-based project was launched by CCSP in 2012 to enhance medication adherence of Medicaid patients with chronic conditions such as diabetes, cardiovascular diseases, respiratory conditions, and mental health conditions; to improve quality of care; and to reduce health care costs in the long term. A collaborative team of providers, pharmacists, and care managers worked together to provide medication management services and improve patient adherence. North Carolina Medicaid patients with prescription drug claims between January 1, 2012, and May 31, 2013, for chronic conditions such as diabetes, hypertension, hyperlipidemia, mental health disorders, and asthma were identified using prescription claims data at CCSP, a regional patient-centered medical home network of Community Care of North Carolina (CCNC) serving Medicaid patients in Cabarrus, Rowan, and Stanly counties of North Carolina. CCNC services have been well defined in other publications.^{19,20}

Claims between January 1, 2012, and December 31, 2012, were used to calculate nonadherence as measured using medication gap analysis. Using the medication gap analysis method, patients were classified as nonadherent if they had a gap of more than 30 days between the assumed depletion date of the last refill (last fill date plus the days supply of last fill) and the screening date. We noticed that gap analysis was yielding higher cases of false positives for nonadherence, so the measure for nonadherence using claims data was changed to a PDC index starting January 1, 2013, through May 31, 2013.

Patients were classified as nonadherent using the PDC measure if they had a PDC index less than 80% over 365 days. The PDC index measures the proportion of days with drug coverage in a given therapeutic window. The PDC calculation is based on

FIGURE 2 Study Sample

the prescription fill dates and days supply in the past 365 days. The therapeutic window (denominator) is the number of days between the first fill date and the calculated date of the last fill (the last fill date + days supply of the last fill). The days with drug coverage (numerator) is the summation of the days supply of all fills within that time period. For example, if a patient filled 3 prescriptions of atorvastatin 20 mg in the time window of 120 days during the past year, then PDC of this drug class (antihyperlipidemics) for the patient is 0.75 (90/120). To provide a more accurate measure, chronic medications in the same drug group (based on mechanism of action) were considered interchangeable, regardless of their brand, strength, and form.

The list of therapeutic medication classes is provided in the Appendix (available in online article). Also, patients with only 1 fill within the previous year and who had no fills of supplementary drugs in the same group were excluded from the analysis. Furthermore, patients were required to have continuous enrollment for at least 1 year before the date of contact to assess medication adherence over the year preceding the pharmacy intervention.

Patients included in this analysis were part of a patient-centered medical home project launched by CCSP to enhance medication adherence of Medicaid patients and improve quality of care. A collaborative team of providers, pharmacists trained to perform comprehensive medication reviews, and care managers who had frequently scheduled home visits with patients worked together to provide medication management services and improve patient adherence. Care alerts were

sent to trained pharmacists and care managers in real time to address adherence-related problems, and patients were contacted within 30 days of receiving the care alert.

Pharmacists and care managers prescreened patients for whom they had received alerts by performing a comprehensive medication review using patient pharmacy records, electronic medical record (EMR) data, physician notes, and patient history. Patients who had discontinued medications and switched to generic medications from brand medications, or other therapeutically equivalent medication categories, and patients who had discontinued medications prescribed for acute conditions were excluded from interviews. Patients were then contacted by a pharmacist to assess nonadherence to medications. Patients were asked open-ended questions to understand reasons for nonadherence. Pharmacists and care managers also contacted the prescribers to check if patients were asked by their prescribers to discontinue their medications or switch to other medications. Patients who could not be contacted via telephone even after multiple attempts, changed networks/providers, died, or were no longer covered through Medicaid/dual eligibility patients were excluded from the study.

Main Independent Variable

Patients were dichotomized as being interview-verified nonadherent or adherent according to patient interviews conducted by care managers and pharmacists. Patients who were marked as nonadherent based on refill records, but were compliant as surmised during patient interviews, were considered as

TABLE 1 Proportion of Patients with Interview-Verified Nonadherence Among Those with Suboptimal Adherence by Prescription Claims

Adherence Measure (Total N)	True Positive		False Positive	
	%	(n)	%	(n)
Medication gap analysis (1,730)	33.1	(573)	66.9	(1,157)
Proportion of days covered (1,410)	83.4	(1,176)	16.6	(234)

false positive cases for nonadherence. Conversely, patients who were marked as nonadherent based on claims records and confirmed nonadherence during patient interviews were considered as true positive cases of nonadherence. The unit of analysis to define the positive predictive ability of prescription claims and the reasons for nonadherence was the chronic medication class. The same patient could contribute to multiple nonadherent medications for the purpose of these analyses. For the purpose of comparing the demographic characteristics of true positive and false positive nonadherence cases, the unit of analysis was the individual patient so as to not duplicate records at the patient-drug level. Patients who had at least 1 interview-verified nonadherent chronic medication class were classified as nonadherent patients for this person-level analysis.

Analyses

In the person-level analysis, patients were considered nonadherent if 1 or more medication records were categorized as interview-verified nonadherent. Patient demographic features were tested for any differences between the false positive nonadherent cases and interview-verified nonadherent patients. Demographic comparisons included age, gender, race, ethnicity, average number of drug therapy problems per patient (identified as part of the original intervention to review medication profiles and provide comprehensive medication reviews for drug therapy problem discovery), average number of nonadherent medications per patient, and average number of therapeutic drug classes used in the past 6 months as classified by the Generic Product Identifier system. These variables were selected based on previous literature around factors that can affect adherence levels and availability in administrative data.^{11,21,22} Univariate associations were explored using t-test, approximate t-test (when variance is not equal), and chi-square tests.

Based on the information collected during open-ended interviews with patients to understand reasons of discontinuation of medications, we created exploratory common themes (Figure 1) to understand the various reasons for nonadherence. We extracted data collected from interviews to understand reasons for nonadherence and classified them into 2 common themes: *patient-related factors* for nonadherence and *external factors*.

Patient-related factors included side effects/adverse events, belief system, education, socioeconomic issues, and miscellaneous factors. Reasons for nonadherence related to side effects/adverse events included medication-related side effects or concern for potential side effects. Motivational issues, patient disbelief in drug effectiveness, discontinuation of medication after relief of symptoms (described as “feeling better after taking medications” by the patient), or discontinuation of medications due to patient feeling worse after taking the medication were included as reasons for nonadherence related to patient belief system. Education-related reasons for nonadherence included poor patient understanding of the disease or drug, inadequate knowledge about drug administration technique, and patient unawareness about change in medications. Socioeconomic issues related to nonadherence included cost barriers such as high cost of medication or limited transportation. Miscellaneous factors included reasons such as complex regimens, patient forgetfulness, drug allergies, and other unspecified reasons.

The external factors included those related to the provider, the pharmacy or health system, and miscellaneous. Issues such as medication name/medication dose/frequency/duration discrepancies and medication omission were included under provider-related factors. Transcription errors, rejected claims, system failure, and unclear or incomplete orders were some of the examples of issues related to the pharmacy or health system. Miscellaneous factors included reasons such as lost prescriptions, expired or damaged medications, and other unknown reasons. The number and percentage of patients in each subgroup were reported. A list of common medications with adherence-related issues based on prescription claims were identified. The proportion of true positive and false positive nonadherent cases for these medications were calculated.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 3,298 patients, with overall 5,362 patient-drug classifications, were identified as nonadherent based on prescription drug claims. Of those, 1,151 (34.9%) patients (corresponding to 1,253 patient-drug classification combinations) were excluded by pharmacists or care managers during prescreening for acute medications or therapeutic substitutions. The remaining 2,147 patients were contacted for interviews with the pharmacist/care manager via telephone, practice encounters, or home visits to examine reasons for nonadherence. Of those, 722 (33.6%) patients were excluded from our analysis because they could not be contacted after multiple attempts, changed providers, or died. Included in the final analysis were 1,425 patients, representing 3,015 medication records (2,936 patient-drug classification combinations). Figure 2 is a flowchart explaining the inclusion-exclusion criteria and final sample size.

TABLE 2 Characteristics of Nonadherent Patients as Identified by Gap Analysis and PDC

Characteristics	Medication Gap Analysis		PDC	
	Interview-Verified Nonadherent Patients (n = 345)	Patients Inaccurately Classified as Nonadherent (n = 694)	Interview-Verified Nonadherent Patients (n = 457)	Patients Inaccurately Classified as Nonadherent (n = 101)
Age, mean (SD)	34.21 (20.32)	31.97 (22.40)	32.25 (21.85) ^b	24.11 (20.04) ^b
Adult patients, n (%)	230 (66.70) ^a	412 (59.40) ^a	271 (59.30) ^b	41 (40.60) ^b
Female, n (%)	211 (61.20)	388 (55.90)	269 (58.90) ^a	46 (45.50) ^a
Race, n (%)				
White	216 (62.60) ^a	422 (60.80) ^a	256 (56.00)	67 (66.30)
Black	117 (33.90) ^a	214 (30.80) ^a	171 (37.40)	26 (25.70)
Other	12 (3.50) ^a	58 (8.40) ^a	30 (6.60)	8 (7.90)
Hispanic	6 (1.70)	24 (3.50)	10 (2.20)	3 (0.50)
Average number of drug therapy problems per patient, mean (SD)	1.41 (0.72) ^b	1.11 (0.34) ^b	1.71 (1.02) ^b	1.00 (0.00) ^b
Average number of medications per patient identified as nonadherent in claims data, mean (SD)	2.08 (1.68) ^b	1.39 (0.88) ^b	2.81 (2.57) ^b	1.22 (0.54) ^b
Average number of therapeutic drug classes in the past 6 months, mean (SD)	1.97 (1.48) ^b	1.38 (0.87) ^b	2.38 (2.19) ^b	1.22 (0.54) ^b

^aStatistically significant difference at $P < 0.05$.^bStatistically significant difference at $P < 0.01$.

PDC = proportion of days covered; SD = standard deviation.

Of the 2,936 patient-drug classification combinations, 2,112 (71.93%) were verified as nonadherent (true positives) based on patient interviews. For the remaining 824 (28.07%) patient-drug classification combinations, patients reported either receiving medications through alternate channels or appropriately discontinued their medication following the advice of their prescribers. Thus, these records were false positives for nonadherence as measured through prescription claims data. The positive predictive value of the claims records was 0.72.

Among interview-verified nonadherent medications, the most common medications were asthma medications such as fluticasone/salmeterol, montelukast, budesonide/formoterol, beclomethasone; oral hypoglycemics such as metformin; and antihypertensive medications such as lisinopril, clonidine, furosemide, hydrochlorothiazide, and amlodipine. Together, these drug classes accounted for about 44% of suboptimal adherence regimens.

At a patient level, 773 patients (54%) confirmed being nonadherent to at least 1 medication and were considered as interview-verified nonadherent patients. The proportion of patients identified as nonadherent by gap analysis and PDC are reported in Table 1. Baseline demographic characteristics of nonadherent patients are presented in Table 2. About 59% of these patients were adults (aged 18 years and older), and about 57% were females. Patients who were not confirmed as nonadherent through interviews were not statistically significantly different than the interview-verified nonadherent patients with regards to age, gender, Hispanic ethnicity, or average number of therapeutic categories of medications used by the patients in the last

6 months. However, interview-verified nonadherent patients had a significantly higher number of drug therapy problems and were on average nonadherent to more number of medications than those not confirmed as nonadherent through interviews.

The patient-reported reasons for nonadherence in adults and caregiver-reported reasons in the pediatric population are presented in Table 3. Self-reported reasons for suboptimal adherence included lack of belief in the drug effectiveness, lack of knowledge about the disease state and medications, inadequate understanding of directions and administration techniques, complex regimens, concern for potential side effects, motivation issues, patient could not remember to take medications, high costs, and limited transportation. Patients also reported discontinuation of chronic medications after they started feeling better. Some of the external barriers reported by nonadherent patients included rejection of claims, transcription errors, lost prescriptions, and expired medications.

Patients who reported discontinuation of their medications due to change in directions, drug allergies, drug interactions, therapeutic duplication, or potential for severe adverse drug reaction were considered as false positive nonadherence cases, since these reasons were deemed to be appropriate reasons for discontinuation. A small percentage of patients reported receiving medications through alternate channels such as free prescriber-provided samples.

Discussion

Our main study findings were (a) prescription claims data may not reflect the true adherence of a patient; (b) appropriate

TABLE 3 Self-Reported Reasons for Nonadherence Among Patients Identified as Nonadherent Using Pharmacy Claims and Verified Through Patient Interviews

Reason for Nonadherence	Aged 0-17 Years		Aged 18 Years and Over	
	n (465)	% 26.50	n (1,284)	% (73.41)
Patient-level factors				
Side effects				
Concern for potential side effects	10	2.15	34	2.65
Side effects	2	0.43	49	3.82
Belief system				
Disbelief in drug effectiveness/does not think medication will help	15	3.23	54	4.21
Lack of motivation to take medications	6	1.29	32	2.49
Patients felt better after taking medication and didn't need it	7	1.51	14	1.09
Patients felt worse after taking medication	0	0.00	3	0.23
Patient education				
Poor understanding of drug or illness	38	8.17	69	5.37
Misunderstood directions	17	3.66	26	2.02
Patient unaware of medication change	2	0.43	9	0.70
Administration technique inadequate	22	4.73	28	2.18
Socioeconomic issues				
Could not afford medication	3	0.65	108	8.41
Cost barrier	2	0.43	89	6.93
Limited transportation	16	3.44	50	3.89
Miscellaneous				
Memory/cannot remember to take medications	8	1.72	27	2.10
Regimen too complex	0	0.00	2	0.16
Does not have/did not have	7	1.51	121	9.42
Patient overusing medications	12	2.58	22	1.71
Patient underusing medications	129	27.74	191	14.88
No specific reason	101	21.72	219	17.06
External factors				
Pharmacy/health system-related issues				
System failure (i.e., rejected claim)	13	2.80	11	0.86
Expired/damaged medications	5	1.08	3	0.23
Miscellaneous				
Lost prescription	1	0.22	0	0.00
Need additional refills	25	5.38	61	4.75
Unknown reason	24	5.16	62	4.83

discontinuation of medications based on physician directions was one of the major reasons for patients to be incorrectly classified as nonadherent in prescription claims data; and (c) patient-related factors were more likely to affect adherence.

Our study represents a validation of prescription claims data for adherence measures compared with the patient interviews. Although we used validated approaches (modified PDC and gap analysis) to identify nonadherence using a prescription claims database, we still found discrepancies in the adherence level of patients when compared with patient responses during interviews. We found that the concordance between the definition of nonadherence of prescription claims and patient interviews was moderate. Almost 40% of the patients who were classified as nonadherent in claims data had either discontinued the medication because of prescriber instruction

or were receiving medication through alternate channels. Of these 40%, a majority of patients (80.37%) who appropriately delayed or discontinued the medication (due to reasons such as changed physician directions, allergies, or drugs interactions) were considered to be adherent to their regimens, while the remaining patients obtained their medications through alternate sources. If one has to look at the effect of alternate sources of medication procurement on the validity of prescription claims, a modest number of patients (7.81%) were misclassified as nonadherent. The reasons for alternative sources could be \$4 generics, physician-provided samples, out-of-pocket payments, and supplemental insurance.

We further investigated the variation in the definition of nonadherence among most common medications. The most common medications to which patients were nonadherent

were asthma drugs and drugs related to other common chronic conditions, such as diabetes and hypertension. More patients were verified as nonadherent to asthma medications, such as fluticasone/salmeterol, montelukast, budesonide/formoterol, and beclomethasone, during patient interviews. The most common reasons for nonadherence in these patients were lack of understanding of disease state and medications. Also, most of these patients were pediatric asthma patients. A study conducted by Sleath et al. (2010) using a pediatric asthma population reported that 87% of the children and their caregivers had issues understanding the directions on the medications and remembering to take the recommended doses.²³ On the other hand, medications such as clonidine, furosemide, and hydrochlorothiazide, which have \$4 generics available, had a higher proportion of adherent patients.²⁴ Thus, prescription drug claims may underestimate adherence in medications that have cheaper alternate channels of procurement.

Among interview-verified nonadherent medication records, we also investigated the reasons for nonadherence. Although, patients were enrolled in North Carolina Medicaid's prescription drug benefit program, which has lower copays, cost-related nonadherence was one of the most commonly reported reasons among the patient-related factors for nonadherence (37.84%). One possible explanation for this could be that cost-related nonadherence is known to be influenced by patient beliefs and perceived value of prescription drugs, so decisions about cost-related nonadherence could be driven by secondary factors such as characteristics of the medication, physical and mental health of the patient, and patient demographics.²⁵ Providers could help improve adherence in these patients by selecting medications from preferred drug lists with lower copayments, prescribing 90-day supplies for chronic medications, and reducing pill burden via dose simplification.

Poor understanding of treatment regimen, poor disease state knowledge, and patient beliefs about efficacy and side effects of medications were some of the other reasons for nonadherence. Poor knowledge about disease management is known to affect a patient's self-efficacy and could lead to lack of motivation to be adherent to medications.^{25,26} It also affects a patient's ability to understand treatment regimen and the directions to take prescribed medications.²⁷ Both of these were listed as reasons for nonadherence in our study. Interventions aimed to improve health literacy and disease knowledge could be a useful strategy to improve adherence.

Limitations

Although our study adds an estimate of the predictive ability of prescription claims data in measuring adherence to the literature, we need to account for some limitations while interpreting these results. One of the limitations of our study was

that we used only gap analysis and modified PDC as measures to classify patients as nonadherent. Although these have been well-accepted methods for identifying nonadherent patients, there are other ways of classifying nonadherent patients based on claims records, such as medication possession ratios.²⁸ These methods may have better predictive ability to identify nonadherent patients.

Patient interviews were used as a standard to compare the prescription claims. Although patient interviews have the ability to capture information on medications that have been obtained through alternate sources (\$4 generics, prescriber sample, over the counter), patients interviews are also prone to recall bias/surveillance bias. We tried to overcome this limitation by also contacting the prescribers and doing EMR reviews.

Although our study was limited to assessing the validity of prescription claims data among patients who were already identified as nonadherent, we did not assess the accuracy of prescription claims data for patients who were identified as adherent using gap analysis and modified PDC. Finally, the study population consisted of continuously enrolled Medicaid populations. These findings may not be generalizable to other populations or other insurance claims data.

Conclusions

Prescription claims can underestimate adherence in patients. The major reason for misclassification of nonadherence status by prescription claim records was appropriate discontinuation of medication as per prescriber directions. To determine the overall accuracy of prescription claim data, further analysis is required to assess the accuracy of prescription claims in identifying truly adherent patients among those who are identified as adherent by claims data. Caution should be taken while interpreting the effectiveness of adherent medication regimens when prescription claims data are used.

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DISCLOSURES

No outside funding supported this study. Glassberg and Wei were employees at Community Care of North Carolina when this research was conducted. Trygstad is an employee of Community Care of North Carolina; Robinson is an employee of Community Care of Southern Piedmont, a subsidiary of Community Care of North Carolina. The geographies, health care professionals, and subjects involved in the study were related to the care coordination work that Community Care of North Carolina was charged with implementing through its informatics and subject matter expertise assistance provided to these local entities to augment primary care activities.

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APPENDIX List of Therapeutic Drug Classes

Drug Class Description	Condition	Drug Class Description	Condition
Antiarrhythmics	Cardiac	Antidepressants—combo	Mental health
Antianginal agents (non-nitrates)	Cardiac	Antidepressants—modified cyclics	Mental health
Antiadrenergic agents	Cardiac	Antipsychotics—second generation	Mental health
Renin inhibitors	Cardiac	Antipsychotics—first generation	Mental health
Angiotensin-converting enzyme inhibitors	Cardiac	ADHD drugs	Central nervous system
Angiotensin II receptor antagonists	Cardiac	Antidementia agents—ACHE inhibitors	Central nervous system
Calcium channel blockers	Cardiac	Inhaled corticosteroids	Respiratory
Insulin	Diabetes	Vasopressors	Cardiac
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Diabetes	Alpha-beta blockers	Cardiac
Sulfonylureas	Diabetes	Beta blockers	Cardiac
Biguanides	Diabetes	Antihyperlipidemics	Hyperlipidemic
Alpha-glucosidase inhibitors	Diabetes	Antiplatelet drugs	Coagulation
Thiazolidinediones	Diabetes	Thyroid agents	Endocrine
Vitamin D	Other	Bone density regulators—parathyroid hormone	Endocrine
Gout agents	Other	Hyperparathyroid treatment—vitamin D analogs	Endocrine
Ulcer drugs	Gastrointestinal	Bone density regulators—bisphosphonates and calcitonins	Other
Antihyperlipidemics—Bile acid sequestrants	Hyperlipidemic	Selective estrogen receptor modulators (SERMs)	Other
Digestive enzymes	Gastrointestinal	Thiazide diuretics	Diuretic
Contraceptives	Other	Potassium sparing diuretics	Diuretic
Antidementia agents—NMDA receptor antagonists	Central nervous system	Selective aldosterone receptor antagonists (SARAs)	Cardiac
Monoamine oxidase inhibitors (MAOIs)	Mental health	Loop diuretics	Diuretic
Antimanic agents	Mental health	Prostatic hypertrophy agents	Genitourinary
Selective serotonin reuptake inhibitors (SSRIs)	Mental health	Anti-IgE monoclonal antibodies	Respiratory
Antiparkinson agents	Central nervous system	Leukotriene modulators	Respiratory
Antidepressants—alpha-2 receptor antagonists	Mental health	Anticonvulsants	Central nervous system
Antidepressants—serotonin-norepinephrine reuptake inhibitors (SNRIs)	Mental health	ADHD stimulants	Central nervous system