

Drug Use Evaluation: Duplicate Drug Therapy

Plain Language Summary: Do Medicaid providers regularly prescribe two or more similar medicines together that do not have additional health benefits?

- Medicines that work in a similar way are grouped together under one drug class name (for example, “statins” and “beta-blockers”). Providers often prescribe medicines from different drug classes to treat their patient’s health condition. There is usually no good reason to use two medicines from the same class because there is no added health benefit and it may increase harmful side-effects. Using two medicines at once from the same drug class to treat a health condition is known as “duplicate drug therapy.”
- In Oregon Medicaid, most patients do not have duplicate drug therapy. Only 1.3% of Oregon Medicaid patients regularly received 2 or more medicines from the same drug class.
- When patients had 2 or more prescribers, it was more common to see patients being treated with duplicate drug therapy compared to one drug therapy.
- When prescriptions were filled at more than one pharmacy, it was more common to see patients being treated with duplicate drug therapy compared to one drug therapy.
- Average healthcare costs (Medical, Pharmacy, and Total) were about twice as much for patients who regularly received duplicate drug therapy compared to those being treated with single drug therapy.

Research Questions:

1. In the Oregon Health Plan (OHP), how many patients are prescribed chronic duplicate drug therapies compared to patients receiving monotherapy?
2. How often is duplicate drug therapy prescribed from more than one provider for 90 days or longer?
3. How often is duplicate drug therapy dispensed from more than one pharmacy for 90 days or longer?
4. Do patients on chronic duplicate drug therapy have a higher impact on healthcare resource utilization compared to patients receiving monotherapy?

Conclusions:

- Patients prescribed chronic duplicate drug therapy compared to patients receiving monotherapy:
 - Only 1.3% of patients from select therapeutic drug classes had chronic duplicate therapy compared to chronic monotherapy.
 - About 9% of patients with chronic duplicate therapy were American Indian or Alaska Native.
 - The relative proportion of American Indian or Alaska Native persons with chronic duplicate therapy compared chronic monotherapy was slightly higher than those without tribal affiliation (1.7% vs 0.3%, respectively).
 - Among standard therapeutic classes, skeletal muscle relaxants had the highest rates of duplicate therapy (8.5%) but the total number of individuals on chronic therapy with SMRs was relatively low (117 patients) over the course of a year.
 - Among drug classes with similar pharmacology, the incretin-based therapies had the highest relative percentage of individuals on chronic duplicate therapy (6%), but the overall number of individuals on chronic incretin therapies was relatively low (47 patients) over the one-year timeframe.

- Patients prescribed chronic duplicate drug therapy from more than one provider:
 - About 59% of patients prescribed chronic duplicate therapy had their prescriptions written by a single prescriber.
 - More patients with 2 or more prescribers had duplicate therapy compared to monotherapy (41% vs. 23%, respectively).
 - Only about 2% of FFS patients had duplicate therapy from 2 or more prescribers.
- Patients prescribed chronic duplicate drug therapy dispensed from more than one pharmacy:
 - About 82% of patients prescribed chronic duplicate therapy had their prescriptions filled at a single pharmacy.
 - More patients who went to 2 or more pharmacies were on duplicative therapy than patients on monotherapy (18% vs. 13%, respectively)
 - Only about 2% of duplicate therapy FFS claims were dispensed from 2 or more pharmacies.
- Patients prescribed chronic duplicate drug therapy and impact on healthcare resource utilization:
 - Mean healthcare costs for patients with chronic duplicate therapy were about twice as much as those with monotherapy within most major categories (Medical, Pharmacy, and Total).
 - Mean costs for outpatient services were about 50% higher for chronic duplicate therapy patients compared to monotherapy.

Recommendations:

- No policy changes recommended.

Current Policy

The Oregon Health Authority's (OHA) Division of Medical Assistance Programs routinely reviews the drug therapy profiles of OHP FFS clients for clinically appropriate drug utilization. The purpose of the polypharmacy profiling program is to work with the client's prescribing practitioner to improve the health and safety of recipients and offer opportunities to enhance continuity and coordination of care in the use of prescription drugs. A key component in the assessment of appropriate drug therapy criteria includes, but is not limited to, therapeutic drug duplication.

Background

It is estimated that about half of the U.S. population has used one or more prescription drugs in the past 30 days.¹ The most commonly prescribed drug classes in adults are lipid-lowering agents, beta-blockers, anti-diabetic drugs, antidepressants, and analgesics.¹ In 2020, U.S. pharmaceutical expenditures grew to \$535 billion, an increase of almost 5% compared to the year before.² As more prescription drugs are consumed, the risk of medication-related harms may be exacerbated by increased patient complexity, disjointed care, multiple prescribers, and low health literacy.³ Medication errors have been defined as a failure in the treatment process that leads to, or has the potential to lead to, patient harm.⁴ A medication error may occur in any part of the medication process including prescribing a patient the wrong type, incorrect dose, route, or preparation of medication, or even a failure to properly monitor the effects and safety of an administered or prescribed medication.⁴ Outpatient medication errors may lead to adverse events that require emergency department visits or unplanned hospitalizations.⁴ It has been estimated that medication-related adverse events (MRAEs) in the U.S. have a healthcare economic impact between \$77 to \$177 billion.⁴

Duplicate prescriptions or written orders for the same or similar medication not intended to be taken simultaneously by the patient may be considered an inappropriate medication error.⁴ However, there are instances when multiple medications prescribed for a patient may be clinically appropriate if each drug has a clear indication, and the regimens are well tolerated and cost-effective.⁵ The use of multiple drugs by an individual is known as polypharmacy.^{6,7} There is no standardized definition for what constitutes polypharmacy but literature consistently suggests the threshold is at least 5 or more medications.⁶⁻⁸ Although polypharmacy may or may not be appropriate, studies in older adults have shown that as the number of drugs prescribed increases, the chance of potentially serious drug-drug interactions (DDI) increase exponentially.⁹ With an excessive number of drugs present on the patient profile, it is a challenge for clinicians to

distinguish between agents prescribed to treat an underlying disease versus those prescribed to treat medication-related side-effects.³ Routine polypharmacy as a result of overprescribing, under-prescribing, or mis-prescribing is clinically inappropriate due to its potential negative impact on adverse drug events, medication adherence, emergency department visits, hospitalizations, and increased direct and indirect healthcare costs.^{3,6,10-12} Some of the most frequently prescribed drugs in a patient with polypharmacy include cardiovascular and metabolic agents.⁶ Age and comorbidity status are common determinants of polypharmacy; however, other sociodemographic factors such as gender, race, ethnicity, place of residence, income level, and behavior may also be key contributors.⁸

Many professional organizations have increasingly recognized the need to promote provider awareness of inappropriate prescribing.^{5,13-15} For patients with advanced age, inappropriate prescribing has been addressed through criterion-based process measures such as the Beers criteria which can be applied to large scale prescribing databases but often lack detail or fail to provide useful clinical alternatives.^{5,13,14} The *Screening Tool of Older Persons potentially inappropriate Prescriptions* (STOPP) is a more comprehensive, physiological-based screening tool which addresses drug-drug and drug-disease interactions, appropriate doses, and treatment duration.¹³ Although the STOPP tool may not be quite as useful for clinicians attempting to optimize drug therapy for younger adults and/or children, it does address important aspects of therapy such as clinical effectiveness and makes suggestions for removal of potentially unnecessary drugs and drug duplications.¹³

In recent years, there has been stronger attempts to reduce unnecessary polypharmacy through deprescribing.⁸ Deprescribing is the planned and supervised process of dose reduction or discontinuing medications that may be causing harm or no longer providing benefit.⁸ Some prescribers may be reluctant to deprescribe based on clinical complexity and fear of destabilizing their patient.¹⁵ When patient care is shared among multiple providers, there may be an unwillingness to deprescribe without awareness of past rationale or due to an incomplete patient history. Other prescribers may still subscribe to a “more is better” treatment philosophy with the belief that deprescribing is denying the patient effective treatment. However, deprescribing considers the potential benefits and harms of each individual drug on the patient’s profile as well as the cumulative risk of multiple drugs used simultaneously.^{15,16} There is mounting evidence to suggest that deprescribing is safe, practical, beneficial, and helps reduce inappropriate drug therapy.^{15,16}

Some types of electronic prescribing software can help alert prescribers to potential inappropriate therapy (i.e., medications prescribed outside of normal age-dose parameters, potentially harmful drug-drug interactions, or possible drug-disease concerns) before the prescription goes to the pharmacy.^{4,17,18} These screening tools may also be designed to alert providers to duplicate drug therapy if present.¹¹ Therapeutic duplication occurs when 2 or more medications from the same therapeutic class are prescribed.^{1,18} Whether simultaneous use of agents from the same drug class or simultaneous use of medications with the same therapeutic effect, duplicate therapy can be dangerous or even deadly for a patient.¹⁸ Studies have reported that therapeutic duplication comprises roughly 6% of all prescribing errors.¹⁹ When patients undergo cross tapers or multiple prescribers become involved in their care, there is a higher potential for unintended therapeutic duplication.²⁰ Medications with different mechanisms from within certain classes such as insulins, antimicrobials, and immunosuppressants may be appropriate; however, other types of therapeutic duplications can present serious problems. For example, duplicate therapy with angiotensin-converting enzyme (ACE) inhibitors may increase the risk of hypotensive symptoms and renal dysfunction without an increase in clinical benefit.²¹ Patients on multiple selective serotonin reuptake inhibitors (SSRIs) or SSRI combined with a selective norepinephrine inhibitor may place the patient at risk of developing anticholinergic effects (urinary retention, constipation, dry mouth, etc.) or even serotonin toxicity.²² Oral anticoagulants have long been ranked among the highest priority for drug safety as well.^{4,23} The Centers for Disease Control and Prevention (CDC) has reported that anticoagulants account for a significant proportion of all emergency department (ED) visits, with typically half of the visits resulting in hospitalization.²³⁻²⁵ Unintended duplicate therapy with anticoagulants can magnify the risks of dangerous hemorrhage especially in patients with advanced age.²⁵ GLP-1 agonists and DPP-4 inhibitors are incretin-based therapies which have not been FDA-approved for combined use, and there are no treatment guidelines or high-quality evidence to recommend additional

benefits of combination therapy.²⁶ With rare cases of acute pancreatitis reported in patients treated with certain incretin-based therapies, it is unknown if duplicate therapy might increase the risk of significant adverse effects.²⁷

Pharmacy claims processing tools are available to help screen profiles to minimize the possibility of dangerous drug duplications.¹⁷ However, pharmacists may not be able to rely exclusively on drug review software to highlight all potentially inappropriate drug therapy duplications.¹⁷ Since computerized claims processing systems often function independently, prescriptions filled at more than one pharmacy increase the risk that therapy duplication will not be identified, especially if multiple prescribers are involved.²⁸ If a therapeutic duplication is identified, the severity or clinical implication may not be available which can hinder pharmacist ability to make informed benefit-risk assessments. Other claims processing software may be programmed with such high sensitivity that legitimate warnings may be ignored due to alert fatigue.²⁷ Whether undetected, overridden or ignored, duplicate therapy of agents with no established clinical benefit is a potential waste of healthcare resources and possibly dangerous.^{12,17,18}

In the fee-for-service (FFS) Medicaid population, studies have reported that almost 50% of members meet the traditional definition of polypharmacy as simultaneous use of 5 or more drugs for a consecutive period of 60 days.⁶ Polypharmacy has been significantly associated with multimorbidity and may result in poorer outcomes and the need for more frequent healthcare utilization.²⁹ The risk of polypharmacy with inappropriate therapeutic duplication may dramatically increase when patient care involves multiple prescribers and pharmacies.²⁸ Certain categories of medications such as antidepressants, anticoagulants, and analgesics may be more prone to duplicate therapy prescribing than others.¹¹ Prior authorizations (PAs) are tools created and enforced by payers to help ensure safe, appropriate, and cost-effective prescribing. However, there may be certain medications or medication-related procedures with clinical, administrative, and/or legal constraints which make the use of PA impractical or inappropriate.³⁰ The purpose of this drug use evaluation (DUE) is to determine how often therapeutic duplication occurs in the Oregon Health Plan (OHP)-FFS population, whether multiple prescribers and or pharmacies are involved, and its impact on overall healthcare costs.

Methods:

This analysis included 2 distinct populations of patients. The first population included any patient with chronic duplicate therapy defined as at least 90 days who were:

- a) covered by 2 or more drugs (based on HSN) within the same specific therapeutic class or
- b) covered by 2 or more agents (HSN) from different specific therapeutic classes (STCs) that have similar mechanisms with no more than a 7-day gap between the dates of service.

The second population included patients with chronic monotherapy with the same definitions except for coverage by only one drug (based on HSN) within the selected specific therapeutic class. The chronic monotherapy population was chosen to provide context for the relative frequency of prescribing for the drug classes of interest.

The primary analysis included continuously eligible FFS and Coordinated Care Organization (CCO) patients with paid FFS claims for drugs of interest (see **Appendix 1, Table A1**) between 1/01/2021 and 12/31/2021.

Patients were excluded if they had primary insurance coverage (i.e., third party liability [TPL]) at any time within the primary analysis period, if they had 75% or less Medicaid eligibility, limited or no Medicaid drug benefit, or Medicare part D coverage at any time during the analysis period. Patients were identified based on the following benefit packages:

Excluded

Category	Benefit Package	Description
Medicare Part D coverage	BMM	Qualified Medicare Beneficiary + Oregon Health Plan with Limited Drug
	BMD	Oregon Health Plan with Limited Drug
	MED	Qualified Medicare Beneficiary
Limited or no Medicaid drug benefit	MND	Transplant package
	CWM	Citizenship Waived Emergency Medical
	SMF	Special Low-Income Medicare Beneficiary Only
	SMB	Special Low-Income Medicare Beneficiary Only

Claims data for these patients may be incomplete. Patients were excluded from the monotherapy group if at any time they had duplicate therapy.

The number of patients prescribed chronic duplicate therapy by a single versus multiple prescribers were evaluated as well as the number of patients with duplicate therapy claims from a single versus multiple pharmacies. Lastly, average patient healthcare costs while on duplicate or monotherapy were assessed for all FFS and CCO claims (pharmacy and medical) paid by Medicaid for a given member during the eligibility period while on duplicate or monotherapy between 01/01/2021 and 12/31/2021.

Results:

Demographics

There were a total of 62,931 patients who were included in these study populations based on paid FFS claims for a drug of interest. Overall for the selected drug classes, there were relatively few patients identified who had chronic duplicate therapy (n=816; 1.3%). Most patients in the primary analysis were between the ages of 19 and 64 years of age. About 9% of all the patients with chronic duplicate therapy were American Indian or Alaska Native (HNA). A larger proportion of members who identified as American Indian/Alaska Native had chronic duplicate therapy compared to the non-HNA population (1.7% vs 0.3%, respectively). Of all the included classes of medications, the SMRs had the highest relative percentage of chronic duplicate therapy (8.5%) but the total number of individuals on chronic therapy with SMRs was relatively low in the FFS population (117 patients). When classes were grouped by similar mechanism, the incretin-based therapies had the highest frequency of chronic duplicate therapy (3 patients; 6%), but only 47 total FFS patients on incretin therapy were identified over a one-year period.

Table 1 - Baseline Therapy Comparison

	# Patients with Chronic Duplicate Therapy		# Patients with Chronic Monotherapy		Percent of Patients on Chronic Duplicate Therapy Relative to Monotherapy (%)
	N=	%	N=	%	
American Indian/Alaska Native (HNA)	70	8.6%	4,000	6.4%	1.7%
Non-HNA	746	91.4%	58,115	93.6%	0.3%
	816		62,115		1.3%

Age					
Avg (min-max)	45.9	(10-67)	39.7	(4-91)	
0-12	1	0.1%	1,338	2.2%	0.1%
13-18	16	2.0%	4,828	7.8%	0.3%
19-64	796	97.5%	55,525	89.4%	1.4%
≥65	3	0.4%	424	0.7%	0.7%
Specific Therapeutic Class					
<i>Inhibitors of RAAS</i>					
A4D		0.0%	572	0.9%	0.0%
A4F		0.0%	262	0.4%	0.0%
A4L		0.0%		0.0%	-
A4T		0.0%		0.0%	-
<i>Incretin based therapies</i>					
C4F		0.0%	1	0.0%	0.0%
C4I		0.0%	34	0.1%	0.0%
C4J		0.0%	9	0.0%	0.0%
<i>Statins (HMG-CoA Reductase Inhibitors)</i>					
M4D	1	0.1%	551	0.9%	0.2%
<i>Statins & Combos (HMG-CoA Reductase Inhibitors and ezetimibe)</i>					
M4M		0.0%		0.0%	-
<i>Beta-Blockers, Oral</i>					
J7A		0.0%	93	0.1%	0.0%
J7C	4	0.5%	314	0.5%	1.3%
<i>Anticoagulants, Oral and SQ</i>					
M9K		0.0%	5	0.0%	0.0%
M9L		0.0%	10	0.0%	0.0%
M9T		0.0%	1	0.0%	0.0%
M9V		0.0%	36	0.1%	0.0%
<i>Antidepressants, SSRIs</i>					
H2S	94	11.5%	44,620	71.8%	0.2%
<i>Antidepressants, SNRIs</i>					
H7C	75	9.2%	15,767	25.4%	0.5%
<i>Muscle Relaxants, Oral</i>					
H6H	10	1.2%	107	0.2%	8.5%

General Mechanism					
Inhibitors of RAAS		0.0%	834	1.3%	0.0%
Incretin-based therapies	3	1.5%	44	0.1%	6.4%
HMG-CoA Reductase Inhib.		0.0%	551	0.9%	0.0%
Beta-blockers	1	0.1%	407	0.7%	0.2%
Anticoagulants		0.0%	52	0.1%	0.0%
Antidepressants	628	77.0%	60,387	97.2%	1.0%

Prescribers

Of the patients identified with chronic duplicate therapy, most (59%) had their prescriptions written by a single prescriber. However, when comparing claims written by 2 or more prescribers, there was a higher percentage of patients with duplicate therapy than monotherapy (41% vs. 23%, respectively). Nonetheless, the occurrence of duplicate therapy with 2 or more prescribers involved was relatively low overall at just over 2% compared to monotherapy with the same agents.

Table 2 - Claims from Single vs. Multiple Prescribers

	# Patients with Chronic Duplicate Therapy		# Patients with Chronic Monotherapy		Percent of Patients on Chronic Duplicate Therapy Relative to Monotherapy (%)
	N=	%	62,115	%	
	816				1.3%
Patients with single prescriber	483	59.2%	47,695	76.8%	1.0%
Patients with ≥2 prescribers	333	40.8%	14,420	23.2%	2.3%

Pharmacies

Most of the patients with chronic duplicate therapy had their prescriptions filled at a single pharmacy (82%). However, there was a relatively higher proportion of patients with duplicate therapy (18%) who filled prescriptions at 2 or more pharmacies than those on monotherapy (13%). Overall, the percentage of duplicate therapy claims dispensed from 2 or more pharmacies appeared to be relatively low (2%) compared to the monotherapy group.

Table 3 - Claims from Single vs. Multiple Pharmacies

	# Patients with Chronic Duplicate Therapy		# Patients with Chronic Monotherapy		Percent of Patients on Chronic Duplicate Therapy Relative to Monotherapy (%)
	N=	%	62,115	%	
	816				1.3%
Patients with single pharmacy	666	81.6%	54,259	87.4%	1.2%
Patients with ≥2 pharmacies	150	18.4%	7,856	12.6%	1.9%

Healthcare Utilization

Mean healthcare costs for patients with chronic duplicate therapy were roughly twice as much as those with monotherapy within most major categories (Medical, Pharmacy, and Total). Outpatient services mean costs were about 50% more for chronic duplicate therapy compared to monotherapy.

Table 4 - Healthcare Resource Utilization while on Duplicate or Monotherapy

	Mean Costs for Patients on Chronic Medications	
	Duplicate Therapy	Monotherapy
Paid Medical Claims		
Emergency Department	\$1,163	\$617
Inpatient Hospitalizations	\$1,048	\$660
Outpatient Services (all other medical claims)	\$21,870	\$14,079
Paid Pharmacy Prescription Claims*	\$2,392	\$1,314
Average Total Costs**	\$26,473	\$16,670

*=Prescription claims include amount paid to pharmacies minus rebates.

**=Average Total Costs include all FFS and CCO claims (pharmacy and medical) paid by Medicaid for a given member category during eligibility period while on duplicate or monotherapy between 01/01/2021 and 12/31/2021.

Limitations:

Data presented in this report is based on OHP claims history and has several inherent limitations.

- The evaluation provides a short “snapshot” in time for agents within a limited number of specific therapeutic classes.
- Data were based on claims history which may not accurately reflect true medication use.
- Patients may elect to pay cash rather than navigate the PA process for certain agents. This evaluation only included claims paid by OHP, and any potential cash claims are not included.
- Medical claims for non-pharmacological services: Due to delays in submission of medical claims and billing mechanisms for non-pharmacological therapies, the mean costs of healthcare resource utilization are difficult to evaluate. Often billing for medical visits is significantly delayed and claims data may not accurately capture all visits. For patients enrolled in a CCO, non-pharmacological treatments, hospitalizations, and ED visits are paid for by the CCO while medication therapy for carve-out medications are paid by FFS.
- Some duplicate therapy claims may have represented dose titrations or specific doses that could not be attained by one commercially available strength or formulation. The DUE did not distinguish whether prescriptions were written by more than one provider while the patient was under transitional care.
- Tribal affiliated claims that received all-inclusive rate (AIR) for reimbursement were not excluded from the total cost figures. Duplicate therapy was identified at a higher frequency in the HNA population. It is unknown as to what extent HNA claims may have resulted in higher pharmacy costs in the duplicate therapy group compared to monotherapy.

References:

1. Martin CB, Hales CM, Gu Q, et al. Prescription drug use in the United States, 2015–2016. National Center for Health Statistics. NCHS Data Brief, no 334. Hyattsville, MD; 2019. Accessed online June 1, 2022.
2. Tichy EM, Hoffman JM, Suda KJ, et al. National trends in prescription drug expenditures and projections for 2021. *Am J Health Syst Pharm*. 2021;78(14):1294-1308.
3. Talebreza S, McPherson ML. Recognizing and Managing Polypharmacy in Advanced Illness. *Medical Clinics of North America*. 2020;104(3):405-413.
4. Laatikainen O, Sneck S, Turpeinen M. Medication-related adverse events in health care-what have we learned? A narrative overview of the current knowledge. *Eur J Clin Pharmacol*. 2022;78(2):159-170.
5. O'Mahony D, Gallagher PF. Inappropriate prescribing in the older population: need for new criteria. *Age and Ageing*. 2008;37(2):138-141.
6. Feng X, Tan X, Riley B, et al. Polypharmacy and Multimorbidity Among Medicaid Enrollees: A Multistate Analysis. *Popul Health Manag*. 2018;21(2):123-129.
7. Petrovic M, O'Mahony D, Cherubini A. Inappropriate prescribing: hazards and solutions. *Age and Ageing*. 2022;51(2):afab269.
8. Talebreza S, McPherson ML. Recognizing and Managing Polypharmacy in Advanced Illness. *Medical Clinics of North America*. 2020;104(3):405-413.
9. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf*. 2007;30(10):911-918.
10. Valuck RJ, Morrato EH, Dodd S, et al. Medicaid Pharmacotherapy Research Consortium. How expensive is antipsychotic polypharmacy? Experience from five US state Medicaid programs. *Curr Med Res Opin*. 2007 Oct;23(10):2567-76.
11. Almodóvar AS, Nahata MC. Associations Between Chronic Disease, Polypharmacy, and Medication-Related Problems Among Medicare Beneficiaries. *Journal of Managed Care & Specialty Pharmacy*. 2019;25(5):573-577.
12. Davies LE, Spiers G, Kingston A, et al. Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. *Journal of the American Medical Directors Association*. 2020;21(2):181-187
13. Bradley MC, Motterlini N, Padmanabhan S, et al. Potentially inappropriate prescribing among older people in the United Kingdom. *BMC Geriatrics*. 2014;14:72.
14. Opondo D, Eslami S, Visscher S, et al. Inappropriateness of Medication Prescriptions to Elderly Patients in the Primary Care Setting: A Systematic Review. *PLOS ONE*. 2012;7(8):e43617.
15. Reeve E, Moriarty F, Nahas R, et al. A narrative review of the safety concerns of deprescribing in older adults and strategies to mitigate potential harms. *Expert Opin Drug Saf*. 2018;17(1):39-49.
16. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA internal medicine*. May 2015;175(5):827-34.
17. Trygstad TK, Christensen D, Garmise J, et al. Pharmacist response to alerts generated from Medicaid pharmacy claims in a long-term care setting: results from the North Carolina polypharmacy initiative. *Journal of Managed Care Pharmacy*. 2005;11(7):575-583.
18. Lee H, Song I, Shin SM, et al. Regulatory effect of decreasing therapeutic duplication of respiratory drugs using a prescription database between 2012 and 2015. *Regulatory Toxicology & Pharmacology*. 2019;103:218-228.
19. Shao SC, Lai EC, Chan YY, et al. Therapeutic Duplication of Long-Acting Injectable Drugs. *Journal of patient safety*. 2018;14(3):e74-e75.
20. Tamblyn RM, McLeod PJ, Abrahamowicz M, et al. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. *Can Med Assoc J* 1996; 154:1177-84.
21. Yusuf S, Teo K, Pogue J, et al. Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *New England Journal of Medicine*. 2008;358(15):1547-1559.
22. Palaniyappan L, Insole L, Ferrier N. Combining antidepressants: a review of evidence. *Advances in Psychiatric Treatment*. 2009;15(2):90-99.

23. Centers for Disease Control and Prevention. Adverse Drug Events from Specific Medicines. 2019. Available from <https://www.cdc.gov/medicationsafety/adverse-drug-events-specific-medicines.html>. Accessed June 1, 2022.
24. Geller AI, Shehab N, Lovegrove MC et al. Emergency Visits for Oral Anticoagulant Bleeding. *J GEN INTERN MED* 35, 371–373 (2020).
25. Rahmzade, R., Cabrera Diaz, F., Zaugg, C. et al. Therapeutic duplication of anticoagulants: a retrospective study of frequency and consequences in a tertiary referral hospital. *Thrombosis J* 18, 14 (2020).
26. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes* 2008;32(Suppl 1):S1-S201.
27. Singh AK, Gangopadhyay KK, Singh R. Risk of acute pancreatitis with incretin-based therapy: a systematic review and updated meta-analysis of cardiovascular outcomes trials. *Expert Rev Clin Pharmacol*. 2020;13(4):461-468.
28. Martin CB, Wiley-Exley EK, Richards S et al. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Annals of Pharmacotherapy*. 2009;43(1):36-44.
29. Priya K, Sreshta M, Philip S. Cost-saving medication therapy management for outpatients. *Perspectives in Clinical Research*. 2021;12(1):14-20.
30. Prada SI, Loaiza JS. Comparing the Medicaid Prospective Drug Utilization Review Program Cost-Savings Methods Used by State Agencies in 2015 and 2016. *American Health & Drug Benefits*. 2019;12(1):7-12.

Appendix 1: Coding Information

Table A1. Codes for Standard Therapeutic Classes

Class	HIC3	HSN	Brand	Generic	PDL
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6113	BENAZEPRIL HCL	benazepril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6113	LOTENSIN	benazepril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	128	CAPOTEN	captopril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	128	CAPTOPRIL	captopril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	130	ENALAPRIL MALEATE	enalapril maleate	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	130	EPANED	enalapril maleate	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	130	VASOTEC	enalapril maleate	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6106	FOSINOPRIL SODIUM	fosinopril sodium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6106	MONOPRIL	fosinopril sodium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	LISINOPRIL	lisinopril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	PRINIVIL	lisinopril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	QBRELIS	lisinopril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	132	ZESTRIL	lisinopril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	9934	MOEXIPRIL HCL	moexipril HCl	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	9934	UNIVASC	moexipril HCl	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	13911	PERINDOPRIL ERBUMINE	perindopril erbumine	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	7631	ACCUPRIL	quinapril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	7631	QUINAPRIL HCL	quinapril HCl	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6080	ALTACE	ramipril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	6080	RAMIPRIL	ramipril	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	8991	MAVIK	trandolapril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4D	8991	TRANDOLAPRIL	trandolapril	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	37444	EDARBI	azilsartan medoxomil	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	16913	ATACAND	candesartan cilexetil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	16913	CANDESARTAN CILEXETIL	candesartan cilexetil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	16920	TEVETEN	eprosartan mesylate	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	15576	AVAPRO	irbesartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	15576	IRBESARTAN	irbesartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	9829	COZAAR	losartan potassium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	9829	LOSARTAN POTASSIUM	losartan potassium	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	23490	BENICAR	olmesartan medoxomil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	23490	OLMESARTAN MEDOXOMIL	olmesartan medoxomil	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	18839	MICARDIS	telmisartan	Y

Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	18839	TELMISARTAN	telmisartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	12204	DIOVAN	valsartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4F	12204	VALSARTAN	valsartan	Y
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4L	42256	ENTRESTO	sacubitril/valsartan	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4T	34493	ALISKIREN	aliskiren hemifumarate	N
Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)	A4T	34493	TEKTURNA	aliskiren hemifumarate	N
Diabetes, DPP-4 Inhibitors	C4F	39970	ALOGLIPTIN-METFORMIN	alogliptin benz/metformin	N
Diabetes, DPP-4 Inhibitors	C4F	34665	JANUMET	sitagliptin phos/metformin	Y
Diabetes, DPP-4 Inhibitors	C4F	34665	JANUMET XR	sitagliptin phos/metformin	N
Diabetes, DPP-4 Inhibitors	C4F	38464	JENTADUETO	linagliptin/metformin HCl	N
Diabetes, DPP-4 Inhibitors	C4F	38464	JENTADUETO XR	linagliptin/metformin HCl	N
Diabetes, DPP-4 Inhibitors	C4F	39970	KAZANO	alogliptin benz/metformin HCl	N
Diabetes, DPP-4 Inhibitors	C4F	37246	KOMBIGLYZE XR	saxagliptin HCl/metformin HCl	N
Diabetes, GLP-1 Receptor Agonists	C4I	40782	ADLYXIN	lixisenatide	N
Diabetes, GLP-1 Receptor Agonists	C4I	38451	BYDUREON BCISE	exenatide microspheres	N
Diabetes, GLP-1 Receptor Agonists	C4I	38451	BYDUREON PEN	exenatide microspheres	N
Diabetes, GLP-1 Receptor Agonists	C4I	32893	BYETTA	exenatide	Y
Diabetes, GLP-1 Receptor Agonists	C4I	44675	OZEMPIC	semaglutide	N
Diabetes, GLP-1 Receptor Agonists	C4I	44675	RYBELSUS	semaglutide	N
Diabetes, GLP-1 Receptor Agonists	C4I	41421	TRULICITY	dulaglutide	Y
Diabetes, GLP-1 Receptor Agonists	C4I	36436	VICTOZA 2-PAK	liraglutide	Y
Diabetes, GLP-1 Receptor Agonists	C4I	36436	VICTOZA 3-PAK	liraglutide	Y
Diabetes, DPP-4 Inhibitors	C4J	39968	ALOGLIPTIN	alogliptin benzoate	N
Diabetes, DPP-4 Inhibitors	C4J	34126	JANUVIA	sitagliptin phosphate	Y
Diabetes, DPP-4 Inhibitors	C4J	39968	NESINA	alogliptin benzoate	N
Diabetes, DPP-4 Inhibitors	C4J	36471	ONGLYZA	saxagliptin HCl	Y
Diabetes, DPP-4 Inhibitors	C4J	37576	TRADJENTA	linagliptin	N
Antidepressants	H2S	10321	CELEXA	citalopram hydrobromide	Y
Antidepressants	H2S	10321	CITALOPRAM HBR	citalopram hydrobromide	Y
Antidepressants	H2S	24022	ESCITALOPRAM OXALATE	escitalopram oxalate	Y
Antidepressants	H2S	1655	FLUOXETINE DR	fluoxetine HCl	V
Antidepressants	H2S	1655	FLUOXETINE HCL	fluoxetine HCl	Y
Antidepressants	H2S	6338	FLUVOXAMINE MALEATE	fluvoxamine maleate	Y
Antidepressants	H2S	6338	FLUVOXAMINE MALEATE ER	fluvoxamine maleate	V
Antidepressants	H2S	24022	LEXAPRO	escitalopram oxalate	Y
Antidepressants	H2S	7344	PAROXETINE CR	paroxetine HCl	V
Antidepressants	H2S	7344	PAROXETINE ER	paroxetine HCl	V
Antidepressants	H2S	7344	PAROXETINE HCL	paroxetine HCl	Y
Antidepressants	H2S	7344	PAXIL	paroxetine HCl	Y
Antidepressants	H2S	7344	PAXIL CR	paroxetine HCl	V
Antidepressants	H2S	25796	PEXEVA	paroxetine mesylate	V

Antidepressants	H2S	1655	PROZAC	fluoxetine HCl	Y
Antidepressants	H2S	6324	SERTRALINE HCL	sertraline HCl	Y
Antidepressants	H2S	6324	TRAZODONE HCL	sertraline HCl	Y
Antidepressants	H2S	6324	ZOLOFT	sertraline HCl	Y
Antidepressants	H7C	26521	CYMBALTA	duloxetine HCl	Y
Antidepressants	H7C	40202	DESVENLAFAXINE ER	desvenlafaxine	V
Antidepressants	H7C	35420	DESVENLAFAXINE SUCCINATE ER	desvenlafaxine succinate	Y
Antidepressants	H7C	26521	DRIZALMA SPRINKLE	duloxetine HCl	V
Antidepressants	H7C	26521	DULOXETINE HCL	duloxetine HCl	Y
Antidepressants	H7C	8847	EFFEXOR	venlafaxine HCl	Y
Antidepressants	H7C	8847	EFFEXOR XR	venlafaxine HCl	Y
Antidepressants	H7C	40632	FETZIMA	levomilnacipran HCl	V
Antidepressants	H7C	35420	PRISTIQ	desvenlafaxine succinate	Y
Antidepressants	H7C	8847	VENLAFAXINE HCL	venlafaxine HCl	Y
Antidepressants	H7C	8847	VENLAFAXINE HCL ER	venlafaxine HCl	Y
Muscle Relaxants, Oral	H6H	1950	AMRIX	cyclobenzaprine HCl	N
Muscle Relaxants, Oral	H6H	1949	BACLOFEN	baclofen	Y
Muscle Relaxants, Oral	H6H	1944	CARISOPRODOL	carisoprodol	N
Muscle Relaxants, Oral	H6H	1942	CARISOPRODOL COMPOUND	carisoprodol/aspirin	N
Muscle Relaxants, Oral	H6H	1941	CHLORZOXAZONE	chlorzoxazone	N
Muscle Relaxants, Oral	H6H	1950	CYCLOBENZAPRINE HCL	cyclobenzaprine HCl	Y
Muscle Relaxants, Oral	H6H	1950	CYCLOBENZAPRINE HCL ER	cyclobenzaprine HCl	N
Muscle Relaxants, Oral	H6H	1947	DANTRIUM	dantrolene sodium	N
Muscle Relaxants, Oral	H6H	1947	DANTROLENE SODIUM	dantrolene sodium	N
Muscle Relaxants, Oral	H6H	1950	FEXMID	cyclobenzaprine HCl	N
Muscle Relaxants, Oral	H6H	1949	FLEQSUVY	baclofen	N
Muscle Relaxants, Oral	H6H	1950	FLEXERIL	cyclobenzaprine HCl	Y
Muscle Relaxants, Oral	H6H	1941	LORZONE	chlorzoxazone	N
Muscle Relaxants, Oral	H6H	1949	LYVISPAH	baclofen	N
Muscle Relaxants, Oral	H6H	1945	METAXALL	metaxalone	N
Muscle Relaxants, Oral	H6H	1945	METAXALONE	metaxalone	N
Muscle Relaxants, Oral	H6H	1938	METHOCARBAMOL	methocarbamol	Y
Muscle Relaxants, Oral	H6H	1936	METHOCARBAMOL W/ASPIRIN	methocarbamol/aspirin	N
Muscle Relaxants, Oral	H6H	1906	NORFLEX	orphenadrine citrate	N
Muscle Relaxants, Oral	H6H	1791	NORGESIC FORTE	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1906	ORPHENADRINE CITRATE	orphenadrine citrate	N
Muscle Relaxants, Oral	H6H	1906	ORPHENADRINE CITRATE ER	orphenadrine citrate	N
Muscle Relaxants, Oral	H6H	1791	ORPHENADRINE-ASPIRIN-CAFF	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1791	ORPHENGESIC	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1791	ORPHENGESIC FORTE	orphenadrine/aspirin/caffeine	N
Muscle Relaxants, Oral	H6H	1949	OZOBAX	baclofen	N

Muscle Relaxants, Oral	H6H	1941	PARAFON FORTE DSC	chlorzoxazone	N
Muscle Relaxants, Oral	H6H	1938	ROBAXIN-750	methocarbamol	Y
Muscle Relaxants, Oral	H6H	1936	ROBAXISAL	methocarbamol/aspirin	N
Muscle Relaxants, Oral	H6H	1945	SKELAXIN	metaxalone	N
Muscle Relaxants, Oral	H6H	1944	SOMA	carisoprodol	N
Muscle Relaxants, Oral	H6H	11582	TIZANIDINE HCL	tizanidine HCl	Y
Muscle Relaxants, Oral	H6H	1944	VANADOM	carisoprodol	N
Muscle Relaxants, Oral	H6H	11582	ZANAFLEX	tizanidine HCl	Y
Beta-Blockers, Oral	J7A	13795	CARVEDILOL	carvedilol	Y
Beta-Blockers, Oral	J7A	34245	CARVEDILOL ER	carvedilol phosphate	N
Beta-Blockers, Oral	J7A	13795	COREG	carvedilol	Y
Beta-Blockers, Oral	J7A	34245	COREG CR	carvedilol phosphate	N
Beta-Blockers, Oral	J7A	2095	LABETALOL HCL	labetalol HCl	Y
Beta-Blockers, Oral	J7A	2095	TRANDATE	labetalol HCl	Y
Beta-Blockers, Oral	J7C	2107	ACEBUTOLOL HCL	acebutolol HCl	Y
Beta-Blockers, Oral	J7C	2104	ATENOLOL	atenolol	Y
Beta-Blockers, Oral	J7C	4791	BETAPACE	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	BETAPACE AF	sotalol HCl	N
Beta-Blockers, Oral	J7C	5168	BETAXOLOL HCL	betaxolol HCl	N
Beta-Blockers, Oral	J7C	7396	BISOPROLOL FUMARATE	bisoprolol fumarate	N
Beta-Blockers, Oral	J7C	2105	BLOCADREN	timolol maleate	N
Beta-Blockers, Oral	J7C	16740	BYSTOLIC	nebivolol HCl	N
Beta-Blockers, Oral	J7C	2103	CORGARD	nadolol	N
Beta-Blockers, Oral	J7C	2101	HEMANGEOL	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	INDERAL LA	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	INDERAL XL	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	INNOPRAN XL	propranolol HCl	N
Beta-Blockers, Oral	J7C	6323	KAPSPARGO SPRINKLE	metoprolol succinate	N
Beta-Blockers, Oral	J7C	5168	KERLONE	betaxolol HCl	N
Beta-Blockers, Oral	J7C	2102	LOPRESSOR	metoprolol tartrate	Y
Beta-Blockers, Oral	J7C	6323	METOPROLOL SUCCINATE	metoprolol succinate	
Beta-Blockers, Oral	J7C	2102	METOPROLOL TARTRATE	metoprolol tartrate	Y
Beta-Blockers, Oral	J7C	2103	NADOLOL	nadolol	N
Beta-Blockers, Oral	J7C	16740	NEBIVOLOL HCL	nebivolol HCl	N
Beta-Blockers, Oral	J7C	2106	PINDOLOL	pindolol	N
Beta-Blockers, Oral	J7C	2101	PROPRANOLOL HCL	propranolol HCl	N
Beta-Blockers, Oral	J7C	2101	PROPRANOLOL HCL ER	propranolol HCl	N
Beta-Blockers, Oral	J7C	4791	SORINE	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	SOTALOL	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	SOTALOL AF	sotalol HCl	N
Beta-Blockers, Oral	J7C	4791	SOTYLIZE	sotalol HCl	N

Beta-Blockers, Oral	J7C	2104	TENORMIN	atenolol	Y
Beta-Blockers, Oral	J7C	2105	TIMOLOL MALEATE	timolol maleate	N
Beta-Blockers, Oral	J7C	6323	TOPROL XL	metoprolol succinate	Y
Statins & Combos	M4D	2793	ALTOPREV	lovastatin	N
Statins & Combos	M4D	12404	ATORVASTATIN CALCIUM	atorvastatin calcium	Y
Statins & Combos	M4D	25009	CRESTOR	rosuvastatin calcium	Y
Statins & Combos	M4D	25009	EZALLOR SPRINKLE	rosuvastatin calcium	N
Statins & Combos	M4D	6312	FLOLIPID	simvastatin	N
Statins & Combos	M4D	8946	FLUVASTATIN ER	fluvastatin sodium	N
Statins & Combos	M4D	8946	FLUVASTATIN SODIUM	fluvastatin sodium	N
Statins & Combos	M4D	8946	LESCOL	fluvastatin sodium	N
Statins & Combos	M4D	8946	LESCOL XL	fluvastatin sodium	N
Statins & Combos	M4D	12404	LIPITOR	atorvastatin calcium	Y
Statins & Combos	M4D	36983	LIVALO	pitavastatin calcium	N
Statins & Combos	M4D	2793	LOVASTATIN	lovastatin	Y
Statins & Combos	M4D	6227	PRAVACHOL	pravastatin sodium	Y
Statins & Combos	M4D	6227	PRAVASTATIN SODIUM	pravastatin sodium	Y
Statins & Combos	M4D	25009	ROSUVASTATIN CALCIUM	rosuvastatin calcium	Y
Statins & Combos	M4D	6312	SIMVASTATIN	simvastatin	Y
Statins & Combos	M4D	6312	ZOCOR	simvastatin	Y
Statins & Combos	M4D	44422	ZYPITAMAG	pitavastatin magnesium	N
Statins & Combos	M4M	26505	EZETIMIBE-SIMVASTATIN	ezetimibe/simvastatin	N
Statins & Combos	M4M	41633	ROSUVASTATIN-EZETIMIBE	ezetimibe/rosuvastatin cal	N
Statins & Combos	M4M	41633	ROSZET	ezetimibe/rosuvastatin cal	N
Statins & Combos	M4M	26505	VYTORIN	ezetimibe/simvastatin	N
Anticoagulants, Oral and SQ	M9K	23233	ARIXTRA	fondaparinux sodium	N
Anticoagulants, Oral and SQ	M9K	7878	ENOXAPARIN SODIUM	enoxaparin sodium	Y
Anticoagulants, Oral and SQ	M9K	23233	FONDAPARINUX SODIUM	fondaparinux sodium	N
Anticoagulants, Oral and SQ	M9K	7429	FRAGMIN	dalteparin sodium,porcine	N
Anticoagulants, Oral and SQ	M9K	8989	INNOHEP	tinzaparin sodium,porcine	N
Anticoagulants, Oral and SQ	M9K	7878	LOVENOX	enoxaparin sodium	Y
Anticoagulants, Oral and SQ	M9L	2812	COUMADIN	warfarin sodium	Y
Anticoagulants, Oral and SQ	M9L	2812	JANTOVEN	warfarin sodium	Y
Anticoagulants, Oral and SQ	M9L	2812	WARFARIN SODIUM	warfarin sodium	Y
Anticoagulants, Oral and SQ	M9T	35604	PRADAXA	dabigatran etexilate mesylate	Y
Anticoagulants, Oral and SQ	M9V	37792	ELIQUIS	apixaban	Y
Anticoagulants, Oral and SQ	M9V	41672	SAVAYSA	edoxaban tosylate	Y
Anticoagulants, Oral and SQ	M9V	35915	XARELTO	rivaroxaban	Y