A Systematic Literature Review Assessing the Directional Impact of Managed Care Formulary Restrictions on Medication Adherence, Clinical Outcomes, Economic Outcomes, and Health Care Resource Utilization

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ABSTRACT

BACKGROUND: There is extensive literature demonstrating that formulary restrictions reduce the pharmacy costs and utilization of restricted drugs. However, some research suggests that there may be unintended consequences of formulary restrictions on other patient outcomes. While several literature reviews have assessed the relationship between formulary restrictions and medication adherence, clinical outcomes, economic outcomes, or health care resource utilization, these reviews were either not systematic, were conducted more than 5 years ago, or did not assess the aggregate directional impact of the relationships.

OBJECTIVE: To conduct a systematic literature review assessing the direction (positive, negative, or neutral) of the relationship between managed care formulary restrictions (including step therapy, cost sharing, prior authorization, preferred drug lists, and quantity limits) on medication adherence, clinical outcomes, economic outcomes, and health care resource utilization.

METHODS: Articles published in 1993 or later were identified from PubMed using 2 lists of search terms. List A included 12 formulary restriction terms and List B included 12 patient outcomes terms, resulting in 144 unique search term combinations. Each article was evaluated by 2 investigators against the following exclusion criteria using a stepwise approach: (a) the article was a commentary or review article; (b) the article did not assess the impact of managed care formulary restrictions on outcomes; and (c) the study was conducted outside the United States. The total number of studies was reported by formulary restriction type. Next, the total number of outcomes reported in each study was summed to conduct an outcomes-level analysis. The outcomes were categorized by type of outcome (medication adherence, clinical, economic, or health care resource utilization) and direction of association (positive, negative, or neutral/not significant) based on the relationship reported in each study. The frequencies of each type of outcome were stratified by direction of association.

RESULTS: A total of 93 studies were included from 811 reviewed articles. Cost sharing was the most commonly assessed type of formulary restriction (60.2% of included articles), followed by prior authorization (21.5%). Of the 262 patient outcomes assessed, medication adherence was the most common (120 outcomes, 45.8%). Overall, formulary restrictions were most frequently negatively correlated with outcomes (130 outcomes, 49.6%). When outcome type was stratified by direction of association, 68.3% (82/120) of medication adherence outcomes were negative. The direction of association of economic outcomes (n=59) with formulary restrictions was split between neutral (37.3%), positive (33.9%), and negative (28.8%). Health care resource utilization outcomes (n=72) had no association with formulary restrictions in 50.0% of the outcomes assessed. There were 11 clinical outcomes identified in the literature review.

CONCLUSIONS: There is a strong evidence base demonstrating a negative correlation between formulary restrictions on medication adherence outcomes. Additional research on commonly used formulary restrictions, specifically prior authorization and step therapy, as well as on the association between formulary restrictions and clinical outcomes, is warranted.

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What is already known about this subject

- Several studies have highlighted unintended consequences of formulary restrictions on patient outcomes. For example, a retrospective study showed that increased cost sharing for antiplatelet therapies was associated with a 22% increase in discontinuation of maintenance therapy, a 26% increase in the risk of hospitalization, and a 38% increase in total medical spending.
- While several literature reviews have assessed the relationship between formulary restrictions and medication adherence, clinical outcomes, economic outcomes, or health care resource utilization, these reviews were either not systematic, were conducted more than 5 years ago, or did not assess the aggregate directional impact of the relationships.

What this study adds

- Formulary restrictions are associated with reduced medication adherence (including discontinuation and persistency) in the existing literature base.
- Despite the evidence that formulary restrictions reduce expenditures of the restricted drug, there is no distinct trend in the direction of association between formulary restrictions and broader economic measures, including total costs, medical costs, and total pharmacy costs.
- Health care resource utilization has no significant association with formulary restrictions in half of the outcomes assessed in the literature.
- There is a paucity of evidence assessing the relationship between formulary restrictions and clinical patient outcomes. Future research should focus on the impact of formulary restrictions on patient health outcomes.

In 2011, the United States spent $2.7 trillion on health care and has maintained a consistent growth rate of 3.9% each year since 2009.[1] Prescription drugs accounted for 9.7% of total health care spending, growing at a lower rate of 0.4%-2.9% compared with other segments of the health care market in recent years. Several factors contribute to the slowed growth of prescription drug spending, including minimal growth in the number of prescriptions dispensed, increased use of generics, patent expirations for brand-name drugs, and increased payer management.[2]

Managed care organizations and pharmacy benefit managers are charged with the task of prescription drug cost control. These organizations, which provide prescription drug benefits for 78% of working Americans, are increasingly using formularies and formulary restrictions in their benefit designs.[3] According to the "Principles of a Sound Drug Formulary System," authored by a consortium of professional organizations, the overall goals of formulary management are to improve patient outcomes and decrease costs by providing safe and appropriate drug therapy.[4] Formulary restrictions are intended to optimize appropriate and efficient utilization of medications. Some of the most commonly used formulary restrictions include cost sharing (copayments, coinsurance, and deductibles); prior authorizations; step therapy; preferred drug lists; and quantity limits.

There is extensive literature demonstrating that these formulary restrictions reduce the pharmacy costs and utilization of the restricted drugs.[5-9] Goldman et al. (2007) conducted a systematic literature review of 132 articles evaluating the impact of cost sharing and found that for every 10% increase in cost sharing, there was a 2%-6% decrease in prescription drug use or expenditures.[5] Multiple other literature reviews have corroborated Goldman's directional findings but have not reported aggregate quantitative evidence in their results.[6-9] While the intended effects of formulary restrictions on pharmacy costs and utilization have been well documented, each literature review also highlighted evidence of unintended consequences of formulary restrictions on patient outcomes.

Several recent studies have reported unintended consequences of formulary restrictions on patient outcomes.[10-12] A retrospective study conducted in 2010 on antiplatelet therapy reported a 21.6% increase in the discontinuation of maintenance therapy, a 38% increase in total medical spending, and a 26% increase in the risk of hospitalization associated with implementing higher cost sharing.[10] A 2011 study of patients with hypertension taking beta blockers found that patients with the highest copayments were 2.5 times more likely to be nonadherent.[11] A study conducted in a Medicaid population found that imposing copayments was associated with increased emergency room (ER) visits and an increase of total 6-month costs of $2,000 per patient.[12] Additionally, multiple literature reviews have suggested that more research is needed to investigate the potentially unintended consequences of formulary restrictions on patient clinical outcomes, utilization, and total health care spending.[5-7,9,13-15]

Given the growing body of evidence reporting unintended consequences of formulary restrictions, there is a need to assess the literature on the impact of formulary restrictions on patient outcomes. While several literature reviews have addressed this topic, these reviews were either not systematic, were conducted more than 5 years ago, or did not assess the aggregate directional impact of the relationships.[5-7,9,13,15] Therefore, the purpose of this systematic literature review was to assess the direction of the relationship between managed care formulary restrictions on medication adherence; clinical outcomes; economic outcomes (total costs, medical costs, or total pharmacy costs); and health care resource utilization.

Methods

Search Strategy

This systematic literature review was conducted using PubMed, the database maintained by the U.S. National Library of Medicine at the National Institutes of Health. Two lists of search terms were created. List A included 12 formulary restrictions search terms: "step therapy," "fail-first," "step edit," "copayment," "drug coinsurance," "quantity limits," "day supply limits," "formulary restrictions," "tier formulary," "open formulary," "closed formulary," and "prior authorization." List B included 12 patient outcome search terms: "compliance," "adherence," "drug utilization," "switching," "drug cost," "drug spending," "total healthcare costs," "resource utilization," "emergency room (ER) visits," "hospitalization," "office visits," and "outcomes." Each term from List A was paired with each term from List B to create 144 unique search term combinations. The search was limited to articles published after 1993 and written in English. Investigators performed the searches, removed duplicate articles, and hand searched the bibliographies of relevant review articles to compile a complete list of potential articles.

Study Selection

Each article identified was evaluated by 2 investigators against a set of exclusion criteria using a stepwise approach. The first step excluded opinion papers, commentaries, review articles, literature reviews, and patient surveys. The second step excluded studies that did not evaluate the primary objective of assessing the impact of managed care formulary restrictions on outcomes. Since the objective of this analysis was to assess the impact of managed care formulary restrictions, studies that were not conducted from the perspective of a third-party payer were excluded (e.g., hospital formulary restrictions). The formulary restrictions evaluated in this study were cost sharing (copayment or coinsurance), prior authorization, step therapy, preferred drug lists, and quantity limits. The

outcomes assessed included medication adherence, clinical outcomes, economic outcomes, and health care resource utilization. Medication adherence included compliance, adherence, persistence, and discontinuation. Clinical outcomes included any measure of patient health. Economic outcomes included total costs, medical costs, or total pharmacy costs. Health care resource utilization included physician visits, hospitalizations (inpatient or outpatient), and ER visits. As previously stated, this study did not evaluate the cost or utilization of restricted drugs, since it is well documented that formulary restrictions decrease pharmacy costs and utilization of the restricted drugs.[5-9] The final step excluded studies completed outside the United States.

Synthesis of Results

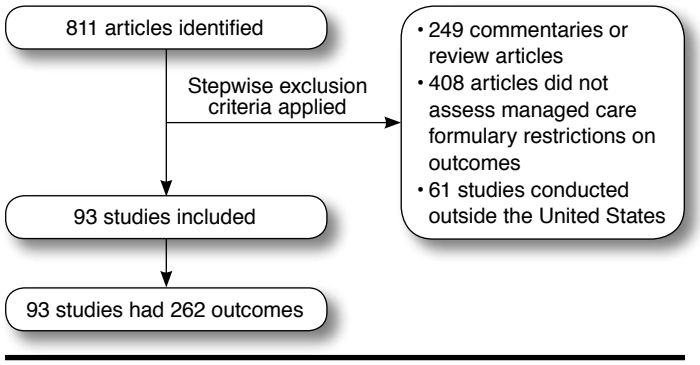
The total number of studies was reported by formulary restriction type and by level of evidence according to the Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services evidence rating. The AHRQ level of evidence is based on the study design and ranges from 1 to 3: *Level I* is the highest level of evidence and includes randomized controlled trials; *Level II-1* is an accurately designed study lacking randomization; *Level II-2* studies are well designed and consist of cohort or case controlled studies; *Level II-3* studies are time series analyses; and *Level III* articles are the opinions of authorities respected in their appropriate fields but based on clinical experience. Level III articles, by definition, were excluded from this literature review.

Next, the total number of outcomes reported in each study was summed to conduct an outcomes-level analysis. Multiple outcomes could be reported in 1 study. The outcomes were stratified by type of outcome and direction of association. The direction of association was determined to be negative if the association between the formulary restriction and outcome was statistically significant and the outcome was worsened (e.g., decreased adherence, worsened clinical outcomes, increased health care utilization, or increased costs). Similarly, the direction of association was positive if the association between the formulary restriction and outcomes was statistically significant and the outcome improved (e.g., increased adherence, improved clinical outcomes, decreased health care utilization, or decreased costs). If there was no statistically significant relationship, the direction was neutral. The frequencies of each type of outcome were stratified by the direction of association.

Results

The initial search strategy resulted in 811 articles, and 93 studies were included in the analysis (Figure 1; see Appendix, which is available in online article, for a more detailed classification of articles). The majority of the studies evaluated cost-sharing restrictions, followed by prior authorization (Figure 2). There were fewer than 10 studies that evaluated each of step therapy, preferred drug lists, and quantity limits. When assessing the level of evidence, the majority of studies were Level II-2 cohort or case controlled studies (n = 61, 65.6%,), followed by Level II-3 time series analyses (n = 31, 33.3%). One randomized controlled trial was included.

FIGURE 1 Study Selection



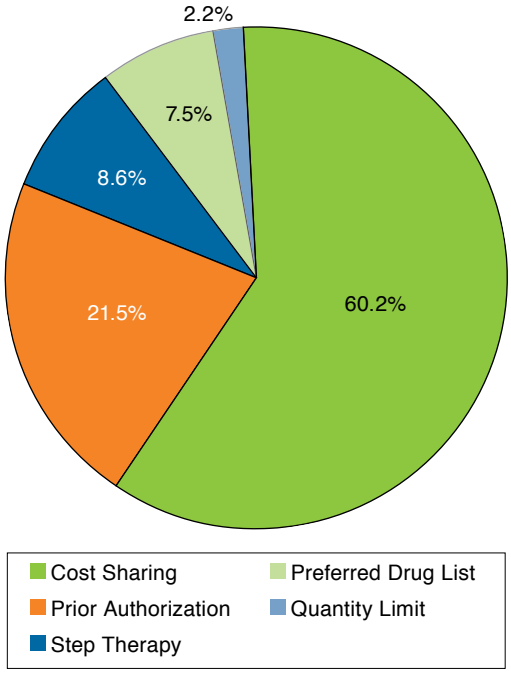
The 93 articles had a total of 262 outcomes. The direction of the association of the 262 outcomes was most commonly negative (49.6% of outcomes) followed by neutral (36.3%; Figure 3). A total of 14.1% of all outcomes were positive. The most common type of outcome assessed was medication adherence (45.8% of outcomes).

When the type of patient outcome was stratified by the direction of association, 68.3% of medication adherence outcomes were negative (Figure 4). Clinical and economic outcomes were distributed in similar proportions between negative, positive, and neutral. Health care resource utilization outcomes had no association with formulary restrictions in 50.0% of the outcomes assessed.

Discussion

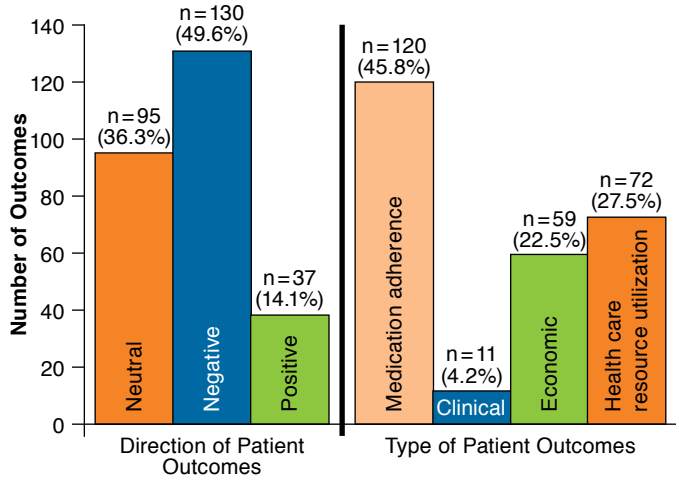
This systematic literature review adds to the existing literature by aggregating the directional impact of formulary restrictions on medication adherence, clinical outcomes, economic outcomes, or health care resource utilization. No previous literature review has been conducted at the outcomes level or provided frequency counts based on the associations from the source studies. Rather, previous literature reviews have generally qualitatively summarized the literature on formulary restrictions.[5-7,9] This has likely been because of the methodological challenges with aggregate quantitative assessments given the vast variety in study designs (pre/post, cohort studies; formulary restrictions; disease states assessed (acute vs. chronic); type of restricted drug (specialty, symptom control); and patient outcomes (type of outcome, measurement of outcome). Goldman et al. published 1 of the few studies to quantitatively assess the impact of cost sharing on drug utilization

FIGURE 2 Distribution of Formulary Restriction Studies[a]



[a]N = 93 studies.

FIGURE 3 Direction and Type of Patient Outcomes[a]



[a]N = 262 outcomes.

and expenditures using elasticity of demand and focusing on a smaller subset of studies.[5] In this subset, every 10% increase in cost sharing decreased prescription drug use and expenditures by 2% to 6%. Our study does not seek to overcome the challenges of aggregating this body of literature; however, we do provide outcomes-level findings with frequencies of the direction of associations from the parent studies. This information is useful in identifying trends in the associations between formulary restrictions and outcomes.

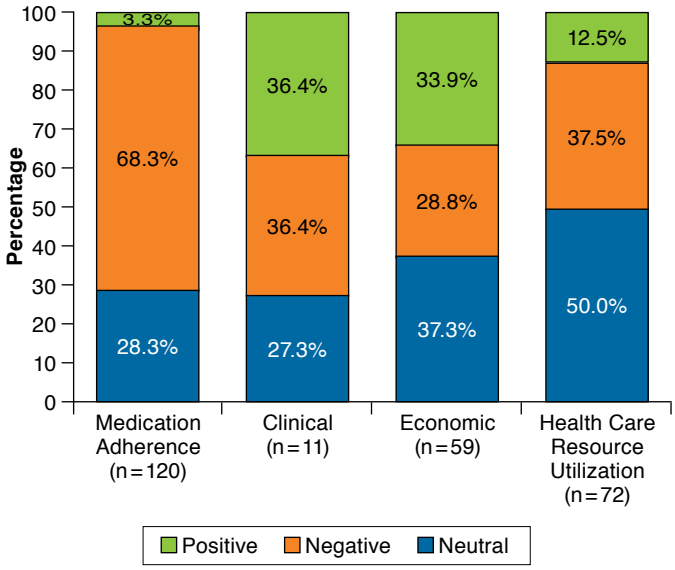
Our study found that the most commonly assessed outcomes were related to medication adherence, of which 68% were negatively associated with formulary restrictions. Previous literature reviews have also concluded that formulary restrictions are associated with worsened medication adherence.[6,9] Additionally, we found that health care resource utilization had no significant association with formulary restrictions in half of the outcomes assessed in the literature, a conclusion substantiated by a prior literature review.[9] Despite the evidence that formulary restrictions reduce expenditures of the restricted drug, we found no distinct trend in the direction of association between formulary restrictions and broader economic measures, including total costs, medical costs, and total pharmacy costs. Prior literature reviews have not reported conclusions regarding the impact of formulary restrictions on medical costs, likely due to the variability in the literature. It should be noted that health care resource utilization and medical costs are directly related; however, not all studies in our literature review evaluated both health care resource utilization and costs. Finally, we identified very few studies that assessed the relationship between formulary restrictions and clinical patient outcomes. This emphasizes the findings of previous literature reviews that called for more research on the implications of formulary restrictions on patient health outcomes.[5,7,9]

An important finding from our study is the lack of research assessing the impact of certain formulary restrictions on medication adherence, clinical outcomes, total costs, total medical costs, total pharmacy costs, and health care resource utilization. It is concerning that prior authorization and step therapy have just 20 and 8 studies, respectively, examining their impact on these outcomes. This is even more imperative since prior authorization is being increasingly used in specialty categories such as growth hormone, rheumatoid arthritis, and hepatitis C.[16] There is an urgent need for managed care to understand the impact of these types of formulary restrictions on outcomes.

Limitations

The findings from this study should be interpreted in the context of the outcomes that were included. As previously stated, pharmacy costs and utilization of the restricted drugs were excluded because their association is well documented in the literature.[5-9] However, total drug costs were included as an economic outcome. Since total drug costs include the cost of the restricted drug, it could be argued that they should not have

FIGURE 4 Direction of Patient Outcomes Stratified by Type of Outcomes[a]



[a]N=262 outcomes.

been included. The rationale for including total drug costs is that restrictions on a given drug may affect spending on other drugs.

There are other limitations to this study. First, the outcomes assessed were measured in different ways across studies. For example, medication adherence could have been measured by abandonment, medication possession ratio, and persistence. These differences may have impacted whether the finding of any given assessment was positive, negative, or neutral. Next, our search strategy did not identify many studies measuring clinical outcomes. This is likely because most of the studies utilized claims analyses, in which it is sometimes difficult to assess clinical endpoints. Therefore, proxies such as health care resource utilization are commonly used. However, it is possible that our search terms failed to identify all of the possible studies on clinical outcomes. Another limitation of our study is the assignment of any given outcome as positive or negative. While this assignment is typically clear (e.g., improved adherence is positive), there are instances where it is not. Specifically, we grouped increases in health care resource utilization (ER, hospitalizations, and physician visits) as negative; however, increased physician visits for chronic disease monitoring may be positive, for example. Finally, patient and provider preference outcomes were not assessed in this study.

Conclusions

Formulary restrictions have become a standard to manage prescription drug spending. However, it is essential that these restrictions be rooted in evidence and that a balance between clinical, economic, and humanistic outcomes is achieved.[17] The findings from this systematic literature review suggest that formulary restrictions are negatively associated with medication adherence. However, there was no distinct trend in the direction of association of economic outcomes with formulary restrictions, and half of health care resource utilization outcomes had no association with formulary restrictions. Additional research on commonly used formulary restrictions, specifically prior authorization and step therapy, as well as on the association between formulary restrictions and clinical outcomes, is needed.

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APPENDIX Study Characteristics (January 1993 to June 2013)

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Included studies evaluating step therapy							
Louder 2011[18]	Step therapy	Inflammation management	Retrospective cohort study	II-2	Clinical	1. Serious GI complications	1. Negative
Mark 2010[19]	Step therapy	Depression	Retrospective cohort study	II-2	Adherence	1. Discontinuation rate	1. Neutral
					Economic	2. ER costs 3. Inpatient costs 4. Outpatient costs 5. Total prescription drug costs	2. Negative 3. Neutral 4. Positive 5. Positive
					Utilization	6. Inpatient admissions 7. ER visits 8. Outpatient office visits	6. Negative 7. Negative 8. Negative
Mark 2009[20]	Step therapy	Hypertension	Pre/post study	II-2	Adherence	1. Discontinuation	1. Negative
					Economic	2. Inpatient medical 3. Outpatient medical	2. Neutral 3. Neutral
					Utilization	4. Inpatient admissions 5. ER visits 6. Outpatient office visits	4. Negative 5. Negative 6. Negative
Panzer 2005[21]	Step therapy	Depression	Simulated cohort study	II-2	Economic	1. Total medical costs 2. Total pharmacy costs	1. Negative 2. Positive
Suehs 2013[22]	Step therapy	Neurology	Retrospective cohort study	II-2	Economic	1. All-cause total health care costs	1. Neutral
					Utilization	2. Outpatient visits 3. ER visits 4. Inpatient visits	2. Neutral 3. Neutral 4. Neutral
Tunis 2006[23]	Step therapy	Antipsychotics	Randomized, open-label trial	II-3	Economic	1. Total costs	1. Neutral
Udall 2013[24]	Step therapy	Neurology	Retrospective cohort study	II-2	Economic	1. Total pharmacy costs	1. Neutral
					Utilization	2. Outpatient utilization	2. Positive
Williams 2012[25]	Step therapy	Type 2 diabetes mellitus	Retrospective cohort analysis	II-2	Clinical	1. Change in HbA1c from pre-index to post-index	1. Negative
					Economic	2. Total medical costs 3. Total pharmacy costs	2. Negative 3. Negative
					Utilization	4. ER visits 5. Inpatient visits 6. Outpatient visits	4. Negative 5. Negative 6. Negative
Included articles evaluating cost sharing							
Balkrishnan 2001[26]	Cost sharing	Multiple	Repeated-measures analytical design	II-3	Economic	1. Total prescription costs 2. Total costs	1. Negative 2. Negative
					Utilization	3. Total outpatient visits 4. Total inpatient/ER visits	3. Positive 4. Positive
Barron 2008[27]	Cost sharing	Type 2 diabetes mellitus	Retrospective cohort study	II-2	Adherence	1. Discontinuation	1. Negative
Borah 2010[28]	Cost sharing	Alzheimer's	Retrospective claims analysis	II-3	Adherence	1. Medication compliance	1. Negative
Briesacher 2007[29]	Cost sharing	Hypertension	Retrospective longitudinal analysis	II-2	Adherence	**Persistence:** 1. ACEIs 2. ARBS 3. Beta blockers 4. CCB 5. Diuretics **Discontinuation rate:** 6. ACEIs 7. ARBS 8. Beta blockers 9. CCB 10. Diuretics	 1. Negative 2. Negative 3. Negative 4. Negative 5. Neutral 6. Negative 7. Neutral 8. Negative 9. Negative 10. Neutral

APPENDIX Study Characteristics (January 1993 to June 2013) *(continued)*

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Brixner 2007[30]	Cost sharing	Multiple	Retrospective time series	II-3	Adherence	**Medication compliance:** 1. Allergic rhinitis 2. Asthma 3. Diabetes mellitus 4. Hypertension 5. Osteoarthritis	 1. Positive 2. Neutral 3. Neutral 4. Neutral 5. Neutral
					Economic	**Total cost:** 6. Allergic rhinitis 7. Asthma 8. Diabetes mellitus 9. Hypertension 10. Osteoarthritis	 6. Neutral 7. Neutral 8. Neutral 9. Neutral 10. Neutral
Burke 2010[31]	Cost sharing	Ischemic stroke	Retrospective cohort study	II-2	Adherence	1. Persistence	1. Negative
Campbell 2011[32]	Cost sharing	Asthma	Retrospective cohort study	II-2	Utilization	**Outpatient visits:** 1. ICS 2. Combo 3. LTRA **ER visits:** 4. ICS 5. Combo 6. LTRA **Asthma hospitalization:** 7. ICS 8. Combo 9. LTRA	 1. Neutral 2. Neutral 3. Neutral 4. Negative 5. Neutral 6. Neutral 7. Negative 8. Negative 9. Negative
Chernew 2008[33]	Cost sharing	Multiple	Individual analysis cohort	II-2	Clinical	**HEDIS measures:** 1. Appropriate asthma medications 2. Beta-blocker use within 7 days	 1. Neutral 2. Negative
					Adherence	3. Depression acute treatment 4. Depression continuous treatment 5. Beta-blocker persistence	3. Neutral 4. Neutral 5. Neutral
Chernew 2008[34]	Cost sharing	-Diabetes mellitus -Congestive heart failure	Econometric models	II-2	Adherence	**Medication compliance:** 1. Low-income patients 2. Medium-income patients 3. High-income patients	1. Negative 2. Negative 3. Negative
Chernew 2008[35]	Cost sharing	Multiple	Quasi-experimental pre/post design	II-2	Adherence	**Medication compliance:** 1. ACE inhibitors 2. Beta blockers 3. Diabetes drugs 4. Statins 5. Steroids	 1. Negative 2. Negative 3. Negative 4. Negative 5. Neutral
Choudhry 2011[36]	Cost sharing	Myocardial infarction	Investigator-initiated, cluster-randomized, controlled policy study	I	Clinical	1. First fatal or nonfatal vascular event or revascularization	1. Neutral
					Adherence	2. Medication compliance	2. Negative
					Economic	3. Total medical cost 4. Total pharmacy cost	3. Neutral 4. Positive
Cole 2006[37]	Cost sharing	Congestive heart failure	Retrospective cohort study	II-2	Adherence	**Medication compliance:** 1. ACE inhibitors 2. Beta blockers	 1. Negative 2. Negative
Choudhry 2010[38]	Cost sharing	-Anticoagulation -Hyperlipidemia	Retrospective cohort study	II-2	Adherence	**Medication compliance:** 1. Anticoagulation 2. Hyperlipidemia	 1. Negative 2. Negative
Colombi 2008[39]	Cost sharing	Diabetes mellitus	Retrospective observational analysis	II-2	Adherence	**Medication compliance:** 1. Low copayment 2. High copayment	 1. Negative 2. Negative
					Economic	**Total health care costs:** 3. Low copayment 4. High copayment	 3. Negative 4. Neutral
					Utilization	**Hospitalizations:** 5. Low copayment 6. High copayment	 5. Negative 6. Neutral

APPENDIX Study Characteristics (January 1993 to June 2013) *(continued)*

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Cooke 2010[40]	Cost sharing	Type 2 diabetes mellitus	Retrospective cohort study	II-2	Adherence	1. Persistence	1. Neutral
Curkendall 2008[41]	Cost sharing	Rheumatoid arthritis	Retrospective cohort study	II-2	Adherence	1. Medication compliance 2. Persistence	1. Negative 2. Negative
Domino 2011[42]	Cost sharing	Multiple	Pre/post controlled partial difference in difference design	II-3	Adherence	**Medication compliance:** 1. Antidepressants 2. Antihypertensive 3. Antipsychotics 4. Antidiabetic 5. Anti-epileptics 6. Statins	 1. Negative 2. Negative 3. Negative 4. Negative 5. Negative 6. Negative
					Economic	7. Total costs	7. Negative
Dor 2010[43]	Cost sharing	Multiple sclerosis	Retrospective cohort study	II-2	Adherence	**Medication compliance:** 1. Copayment cohort 2. Coinsurance cohort	 1. Neutral 2. Negative
Doshi 2009[44]	Cost sharing	Hyperlipidemia	Quasi-experimental study	II-3	Adherence	1. Medication compliance 2. Discontinuation	1. Negative 2. Negative
Ellis 2004[45]	Cost sharing	Hyperlipidemia	Retrospective cohort study	II-2	Adherence	1. Medication compliance 2. Discontinuation	1. Negative 2. Negative
Fairman 2003[46]	Cost sharing	Multiple	Quasi-experimental, pre/post with comparison group design	II-3	Adherence	1. Medication compliance	1. Neutral
					Economic	2. Total pharmacy cost	2. Positive
					Utilization	3. Office visits 4. Inpatient hospitalizations 5. ER visits	3. Neutral 4. Neutral 5. Neutral
Gibson 2006[47]	Cost sharing	Hyperlipidemia	Retrospective cross-sectional time series	II-3	Adherence	1. New users medication compliance 2. Continuing users medication compliance	1. Negative 2. Negative
Gibson 2006[48]	Cost sharing	Hyperlipidemia	Retrospective observational	II-2	Adherence	1. Medication compliance	1. Negative
Gibson 2010[49]	Cost sharing	Antipsychotic	Retrospective observational	II-2	Adherence	1. Medication compliance 2. Discontinuation	1. Negative 2. Negative
Gilman 2008[50]	Cost sharing	Multiple	Cross-sectional cohort	II-2	Economic	1. Total pharmacy cost	1. Positive
Gilman 2007[51]	Cost sharing	Multiple	Multivariate regression analysis	II-2	Economic	1. Total pharmacy costs	1. Negative
Gleason 2009[52]	Cost sharing	Multiple	Observational cross-sectional study	II-2	Adherence	**Drug abandonment:** 1. TNF blocker 2. Biologics	 1. Negative 2. Negative
Goldman 2006[53]	Cost sharing	Hyperlipidemia	Retrospective time series	II-2	Adherence	1. Medication compliance	1. Negative
Gu 2010[54]	Cost sharing	Diabetes mellitus	Retrospective cohort study	II-2	Adherence	**Medication compliance:** 1. Generic coverage cohort 2. No coverage cohort	 1. Negative 2. Negative
Hartung 2008[55]	Cost sharing	Multiple	Retrospective cohort study	II-3	Utilization	1. ER visits 2. Office visits 3. Hospitalizations	1. Positive 2. Positive 3. Positive
Huskamp 2005[56]	Cost sharing	ADHD	Observational study using quasi-experimental design	II-3	Adherence	1. Persistence	1. Neutral
Johnson 1997[57]	Cost sharing	Multiple	Time-series analysis	II-3	Economic	1. Total medical cost	1. Neutral
					Utilization	2. Medical care utilization	2. Neutral
Kessler 2007[58]	Cost sharing	Multiple	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative

APPENDIX Study Characteristics (January 1993 to June 2013) *(continued)*

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Kim 2011[59]	Cost sharing	Multiple	Cox regression analysis	II-2	Adherence	**Medication compliance:** 1. Anti-inflammatory 2. Cancer 3. Immunosuppressant 4. Multiple sclerosis **Persistence:** 5. Anti-inflammatory 6. Cancer 7. Immunosuppressant 8. Multiple sclerosis	 1. Neutral 2. Neutral 3. Neutral 4. Neutral 5. Neutral 6. Neutral 7. Negative 8. Negative
Landsman 2005[60]	Cost sharing	Multiple	Retrospective prescription claims analysis	II-2	Adherence	**Medication compliance:** 1. TCA 2. SSRI 3. Triptan 4. NSAIDS 5. COX-2 6. Statin 7. CCB 8. ARB 9. ACE **Discontinuation:** 10. TCA 11. SSRI 12. Triptan 13. NSAIDS 14. COX-2 15. Statin 16. CCB 17. ARB 18. ACE	 1. Negative 2. Negative 3. Negative 4. Negative 5. Neutral 6. Negative 7. Negative 8. Neutral 9. Negative 10. Neutral 11. Negative 12. Neural 13. Neutral 14. Neutral 15. Negative 16. Neutral 17. Negative 18. Negative
Lurk 2004[61]	Cost sharing	Multiple	Retrospective cohort study	II-3	Utilization	1. Outpatient visits	1. Neutral
Maciejewski 2010[62]	Cost sharing	Multiple	Retrospective cohort study	II-2	Adherence	**Medication compliance:** 1. Oral hypoglycemic agent 2. Antihypertensive 3. Hyperlipidemia	 1. Neutral 2. Positive 3. Positive
Maciejewski 2010[63]	Cost sharing	Multiple	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Motheral 2001[64]	Cost sharing	Multiple	Quasi-experimental pre/post with comparison group design	II-3	Adherence	1. Medication continuation (persistence)	1. Neutral
					Economic	2. Total prescription cost 3. Total cost	2. Positive 3. Positive
					Utilization	4. ER visits 5. Inpatient visits 6. Physician office visits	4. Neutral 5. Neutral 6. Neutral
Neugut 2011[65]	Cost sharing	Breast cancer	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Patterson 2011[11]	Cost sharing	Hypertension	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Pedan 2007[66]	Cost sharing	Hyperlipidemia	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Philipson 2010[10]	Cost sharing	Antiplatelet	Retrospective cohort study	II-2	Adherence	1. Discontinuation	1. Negative
					Utilization	2. Rehospitalizations	2. Negative
					Economic	3. Acute coronary syndrome medical costs	3. Negative
Pugh 2011[67]	Cost sharing	Multiple	Cross-sectional retrospective database analysis	II-3	Clinical	**Drug-disease interactions:** 1. Dementia 2. Fall 3. Chronic renal failure	 1. Positive 2. Positive 3. Positive
Schultz 2005[68]	Cost sharing	Hyperlipidemia	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
					Clinical	2. Low-density lipoprotein cholesterol goal attainment	2. Neutral

APPENDIX Study Characteristics (January 1993 to June 2013) *(continued)*

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Sedjo 2008[69]	Cost sharing	Hyperlipidemia	Quasi-experimental, pre/post design	II-3	Adherence	1. Medication compliance	1. Negative
Shrank 2010[70]	Cost sharing	Multiple	Cross sectional cohort study	II-2	Adherence	1. Abandonment	1. Negative
Subramanian 2011[12]	Cost sharing	Cancer	Retrospective time series study	II-2	Economic	1. Total medical cost	1. Negative
					Utilization	2. ER visits	2. Negative
Taira 2006[71]	Cost sharing	Antihypertensive	Retrospective observational analysis	II-2	Adherence	1. Medication compliance	1. Negative
Wiegand 2012[72]	Cost sharing	Hyperlipidemia	Retrospective database analysis-naive	II-2	Adherence	1. Medication compliance	1. Negative
Yang 2011[73]	Cost sharing	Antihypertensive	Retrospective cohort study	II-2	Adherence	1. Persistence	1. Negative
Ye 2007[74]	Cost sharing	Hyperlipidemia	Longitudinal retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Yoon 2009[75]	Cost sharing	Mulitple	Cross-sectional study	II-2	Adherence	1. Medication compliance	1. Negative
Zeber 2007[76]	Cost sharing	Schizophrenia	Quasi-experimental	II-3	Utilization	1. Psychiatric admissions 2. Outpatient visits 3. Inpatient visits	1. Negative 2. Neutral 3. Negative
					Economic	4. Pharmacy costs	4. Positive
Zeng 2010[77]	Cost sharing	Diabetes	Cohort	II-2	Adherence	1. Medication compliance	1. Negative
Zhang 2007[78]	Cost sharing	Hypertension	Observational cohort study	II-2	Adherence	1. Patient persistence	1. Negative
Included articles evaluating prior authorization							
Abouzaid 2010[79]	PA	Antipsychotic	Cohort study	II-2	Economic	1. Hospitalizations	1. Neutral
Adams 2009[80]	PA	Antidepressants	Interrupted time series and longitudinal data analysis	II-3	Utilization	1. Hospitalizations 2. ER visits	1. Neutral 2. Neutral
Buckley 2010[81]	PA	RSV	Retrospective cohort	II-2	Utilization	1. ER visits 2. Hospitalizations	1. Negative 2. Neutral
					Economic	3. Cost per treatment	3. Negative
Delate 2005[82]	PA	Acid suppression	Interrupted time series/ continued retrospective cohort analysis	II-3	Economic	1. Total pharmacy costs	1. Positive
Farley 2008[83]	PA	Antipsychotics	Interrupted time series	II-2	Economic	1. Pharmacy costs 2. Costs per claim 3. User costs per month	1. Negative 2. Neutral 3. Neutral
Gleason 2005[84]	PA	Inflammation/ pain management	Pre/post cohort	II-2	Economic	1. Pharmacy costs 2. Medical costs	1. Positive 2. Positive
					Utilization	3. Physician outpatient	3. Neutral
Hartung 2006[85]	PA	Multiple	Cost analysis	II-3	Economic	1. Total pharmacy costs	1. Positive

APPENDIX Study Characteristics (January 1993 to June 2013) *(continued)*

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Hartung 2004[86]	PA	Inflammation/ pain management	Retrospective interrupted time-series study	II-3	Utilization	**MCO:** 1. Office visits 2. ER visits 3. Hospitalizations **FFS:** 4. Office visits 5. ER visits 6. Hospitalization	 1. Neutral 2. Negative 3. Neutral 4. Neutral 5. Neutral 6. Neutral
Law 2010[87]	PA	Antihypertensive	Longitudinal population-based study	II-2	Economic	1. Total pharmacy costs	1. Positive
Margolis 2010[88]	PA	Neuropathic pain	Pre/post parallel cohort	II-2	Economic	1. Total costs	1. Neutral
Margolis 2009[89]	PA	Neuropathic pain	Retrospective cohort	II-2	Economic	1. Total medical costs	1. Negative
McCombs 2002[90]	PA	Antidepressants	Retrospective analysis	II-3	Adherence	1. Completion of therapy	1. Neutral
Momani 2002[91]	PA	Inflammation/ pain management	Pre/post time-series study	II-3	Clinical	1. Quality of life	1. Positive
Simeone 2010[92]	PA	Mental health	Secondary analysis	II-3	Economic	1. Pharmacy costs	1. Negative
					Utilization	2. Hospitalizations	2. Neutral
					Adherence	3. Medication compliance	3. Neutral
Siracuse 2008[93]	PA	Inflammation/ pain management	Retrospective cross-sectional study	II-3	Economic	1. Pharmacy costs	1. Positive
Smalley 1995[94]	PA	Multiple	Interrupted time series	II-3	Utilization	1. Outpatient visits	1. Neutral
					Economic	2. Pharmacy costs 3. Medical costs	2. Neutral 3. Neutral
Soumerai 2008[95]	PA	Anitpsychotics	Cohort study	II-2	Adherence	1. Discontinuation	1. Negative
Starner 2012[96]	PA	Diabetes mellitus	Quasi-experimental time-series analysis	II-3	Adherence	1. Antidiabetic compliance	1. Positive
Walthour 2010[97]	PA	Antipsychotics	Single cohort observational study	II-3	Utilization	1. ER visits 2. Office visits 3. Hospitalizations 4. Medicaid withdrawal	1. Positive 2. Positive 3. Neutral 4. Neutral
Zhang 2009[98]	PA	Bipolar	Interrupted time series	II-3	Adherence	1. Discontinuation	1. Negative
Included articles evaluating preferred drug list							
Johnson 2008[99]	Preferred drug list	-Inflammation/ pain management -Osteoarthritis -Rheumatoid arthritis	Retrospective cross-sectional study	II-2	Utilization	**Osteoarthritis:** 1. Ambulatory care visits 2. Hospitalizations 3. ER visits **Rheumatoid arthritis:** 4. Ambulatory care visits 5. Hospitalizations 6. ER visits	 1. Positive 2. Negative 3. Neutral 4. Positive 5. Negative 6. Neutral
					Economic	1. Osteoarthritis costs 2. Rheumatoid arthritis costs	1. Negative 2. Neutral
Lichtenberg 2005[100]	Preferred drug list	Multiple	Retrospective claims analysis	II-3	Clinical	1. Vintage of medications used	1. Negative
Murawski 2005[101]	Preferred drug list	Cardiovascular	Time sequence study	II-3	Utilization	1. Inpatient hospital visits 2. Outpatient hospital visits 3. Physician visits	1. Neutral 2. Negative 3. Negative
					Economic	4. Total costs	4. Neutral

APPENDIX Study Characteristics (January 1993 to June 2013) *(continued)*

Reference	Restriction Type	Disease State	Study Design	Level of Evidence[a]	Outcome Type	Outcome	Direction of Association
Ridley 2006[102]	Preferred drug list	Hyperlipidemia	Retrospective cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Streja 1999[103]	Preferred drug list	Mental health	Cohort study	II-2	Adherence	1. Medication compliance	1. Negative
Wilson 2005[104]	Preferred drug list	Antihypertensive	Retrospective cohort study	II-2	Adherence	1. Discontinuation 2. Switch to unrestricted medication	1. Negative 2. Neutral
Miller 2007[105]	Preferred drug list	-ACE inhibitors -Beta blockers -Calcium channel blockers -Mental health	Pre/post design	II-3	Economic	1. Total pharmacy cost	1. Positive
	Quantity limits					2. Total pharmacy cost	2. Positive
Included articles evaluating quantity limits							
Dunn 2006[106]	Quantity limits	Migraine	Observational study	II-3	Utilization	1. Total number of medical claims	1. Neutral
Hoffman 2003[107]	Quantity limits	Migraine	Retrospective observational study	II-3	Utilization	1. Outpatient visits 2. ER visits 3. Inpatient hospitalizations	1. Positive 2. Positive 3. Positive
					Economic	4. Outpatient payments 5. ER visit payments 6. Inpatient hospital payments	4. Positive 5. Positive 6. Positive

[a]*The AHRQ level of evidence is based on the study design and ranges from 1 to 3: Level I is the highest level of evidence and includes randomized controlled trials; Level II-1 is an accurately designed study lacking randomization; Level II-2 studies are well designed and consist of cohort or case controlled studies; Level II-3 studies are time series analyses; and Level III articles are the opinions of authorities respected in their appropriate fields but based on clinical experience.*

ACE inhibitors = angiotensin-converting enzyme inhibitors; ADHD = attention deficit hyperactivity disorder; anticoagulation = can refer to many disease states; ARB = angiotensin receptor blocker; CCB = calcium channel blockers; Combo = inhaled corticosteroid plus long-acting beta agonist; COX-2 = cyclooxygenase 2; ER = emergency room; FFS = fee for service; GI = gastrointestinal; HbA1c = hemoglobin A1c; HEDIS = Healthcare Effectiveness Data and Information Set; ICS = inhaled corticosteroid; LRTA = leukotriene receptor antagonist; MCO = managed care organization; NSAIDs = nonsteroidal anti-inflammatory drugs; PA = prior authorization; PPIs = proton pump inhibitors; RSV = respiratory syncytial virus; SSRIs = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant, TNF = tumor necrosis factor.