The Effect of Formulary Restrictions on Patient and Payer Outcomes: A Systematic Literature Review

Yujin Park, PharmD; Syed Raza, MS; Aneesh George, MS; Rumjhum Agrawal, MPharm; and John Ko, PharmD, MS

ABSTRACT

BACKGROUND: Formulary restrictions are implemented to reduce pharmacy costs and ensure appropriate use of pharmaceutical products. As adoption of formulary restrictions increases with rising pharmacy costs, there is a need to better understand the potential effect of formulary restrictions on patient and payer outcomes.

OBJECTIVE: To conduct a systematic literature review that assesses the effect of formulary restrictions on the following outcomes: medication adherence, clinical outcomes, treatment satisfaction, drug utilization, health care resource utilization, and economic outcomes.

METHODS: Studies published in 2005 or later were identified from the MEDLINE, Embase, and Cochrane databases and the National Health Service Economic Evaluation Database, using 2 sets of search terms. A total of 17 formulary restriction terms (e.g., step therapy [ST] and prior authorization [PA]) and 55 outcome terms were included, resulting in 935 unique search term combinations. Two reviewers independently conducted analyses of the titles, abstracts, and full-text articles. The search was limited to English-language articles that evaluated the effect of ST and/or PA placed by U.S. third-party payers on the following outcomes: patient outcomes (medication adherence, clinical outcomes, and treatment satisfaction) and payer outcomes (drug utilization, health care resource utilization, and economic outcomes).

RESULTS: Of 2,321 reviewed articles, 59 articles met the study inclusion criteria. The included studies assessed the effect of ST (n = 18), PA (n = 35), or both (n = 6) on medication adherence (n = 14), clinical outcomes (n = 12), treatment satisfaction (n = 2), drug utilization (n = 39), health care resource utilization (n = 18), and economic outcomes (n = 42). The 59 articles measured 164 outcomes across the patient, health care resource utilization, and economic outcome categories of interest. Of the total number of outcomes, 50.6% (n = 83) were negative in direction or were unfavorable, whereas 40.2% (n = 66) were positive in direction or were favorable, when the perspectives of patients and payers were considered. Of the total number of drug utilization outcomes reported (n = 46), the majority showed lower drug utilization (>90%). However, in some of the articles, pharmacy cost savings resulting from lower drug utilization appeared to be offset by increased medical costs.

CONCLUSIONS: Formulary coverage decisions may have unintended consequences on patient and payer outcomes despite lower drug utilization and pharmacy cost savings; therefore, careful evaluation of restrictions before policy implementation and continued reevaluation after implementation is warranted.

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What is already known about this subject

- Formulary restrictions have been shown to reduce drug utilization, leading to pharmacy cost savings; however, the unintended consequences of such restrictions on patients and payers are relatively less understood.
- Although previous literature has summarized the evidence on unintended consequences of formulary restrictions, there is a need to evaluate the comprehensive list of patient and payer outcomes.

What this study adds

- This study evaluated a comprehensive list of patient outcomes (medication adherence, clinical outcomes, and treatment satisfaction) and payer outcomes (health care resource utilization and economic outcomes).
- Formulary restrictions are associated with reduced medication adherence and negative clinical outcomes in patients.
- Although formulary restrictions reduce drug utilization and associated drug costs, resulting in pharmacy cost savings, some of these cost savings may be offset by increased health care resource utilization and medical costs.

Health care expenditure in the United States is increasing every year and more than doubled from the years 2000 to 2015. National health care expenditure in 2015 was approximately $3.2 trillion, and in the same year, expenditure on prescription drugs comprised 10.1% of the national health care expenditure.[1] Increases in health care expenditures are partly related to third-party payment systems because patient perceptions of relatively low out-of-pocket costs has led to increased demand for medical services, thereby driving up costs and creating additional layers of expenditures because of more administrative tasks for providers, employers, and third-party payers.[2] When the Medicare and Medicaid systems first came into existence in the 1960s, out-of-pocket costs were greater than third-party payments; however, since then, there has been a steady increase in the use of third-party payment models and a subsequent decrease in out-of-pocket costs for patients.[3,4]

Because of increasing health care spending in the United States, third-party payers introduced various techniques aimed at controlling rising health care costs, and organizations such

as managed care organizations (MCOs) and pharmacy benefit managers came into existence. These organizations essentially control financing and delivery of health care services, in association with selected providers, by monitoring quality and use of health care services.[5] The purpose of MCOs, pharmacy benefit managers, and employer-sponsored plans is to reduce costs and use of prescription drugs and other health care services, while providing quality service.[6,7]

Regarding prescription drugs, commonly used pharmacy management policies by third-party payers include formulary restrictions through implementation of prior authorization (PA), step therapy (ST) or step edit, cost sharing, cap drug benefits, and preferred drug lists (PDLs).[6] PA involves acquiring advance approval from a health insurance plan before reimbursement can occur for a medication, and ST involves the use of other lower-cost alternatives before payment is authorized by a health insurance plan.[8,9]

Formulary restrictions are designed and implemented to reduce costs and use of prescription drugs[10-13] and have been shown to be effective in a number of literature reviews.[14-18] Motheral (2011) conducted a critical review of the literature,[18] including 14 studies on ST interventions, and concluded that the ST programs resulted in significant pharmacy cost savings and reduced drug utilization. Although all of the reviews evaluated the effect of formulary restrictions on drug utilization and costs, each review also emphasized the importance of identifying the unintended effects of formulary restrictions on outcomes such as drug compliance and clinical, economic, and humanistic outcomes.

Studies have also reported unintended consequences of managed care formulary restrictions on health outcomes.[19-24] Mark et al. (2010) evaluated the effect of ST on antidepressant users in employer plans and reported a 4.7% increase in outpatient office visits, a 17% higher number of inpatient admissions, and a 37% increase in the number of emergency room (ER) visits.[19] A retrospective study conducted by Johnston et al. (2014) assessed the effect of pregabalin PA on clinical outcomes and reported 59.8% higher odds of medication-medication and medication-condition interactions in the pregabalin PA group compared with the non-PA group.[23] Moreover, additional literature reviews have investigated unintended effects of formulary restrictions on outcomes such as clinical outcomes, medication adherence, health care resource utilization, and economic outcomes.[14-16,25,26]

Although previous literature reviews have summarized the evidence on unintended consequences of formulary restrictions for some outcomes, there is a need to evaluate the evidence on the effect of formulary restrictions on a range of outcomes systematically. Although previous literature reviews have delved into this topic, their approach was either not systematic in terms of methodology (e.g., not covering a variety of biomedical databases) or not comprehensive in terms of the range of outcomes evaluated (e.g., medication adherence and clinical, economic, health care resource utilization, and patient-reported outcomes); they also did not assess the overall directional positive or negative impact of the outcomes.[14-16,25] Only 1 recent systematic review assessed the directional effect of formulary restrictions on patient and payer outcomes and evaluated a variety of formulary restrictions, including cost sharing, quantity limits, PDLs, ST, and PA.[26] Considering the increased use of formulary restrictions such as ST and PA, there is a growing need to evaluate their effect on a range of health outcomes; therefore, we aimed to use this systematic literature review (SLR) to assess the effect of PA and/or ST on the following outcomes: medication adherence, clinical outcomes, treatment satisfaction, drug utilization, health care resource utilization, and economic outcomes.

Methods

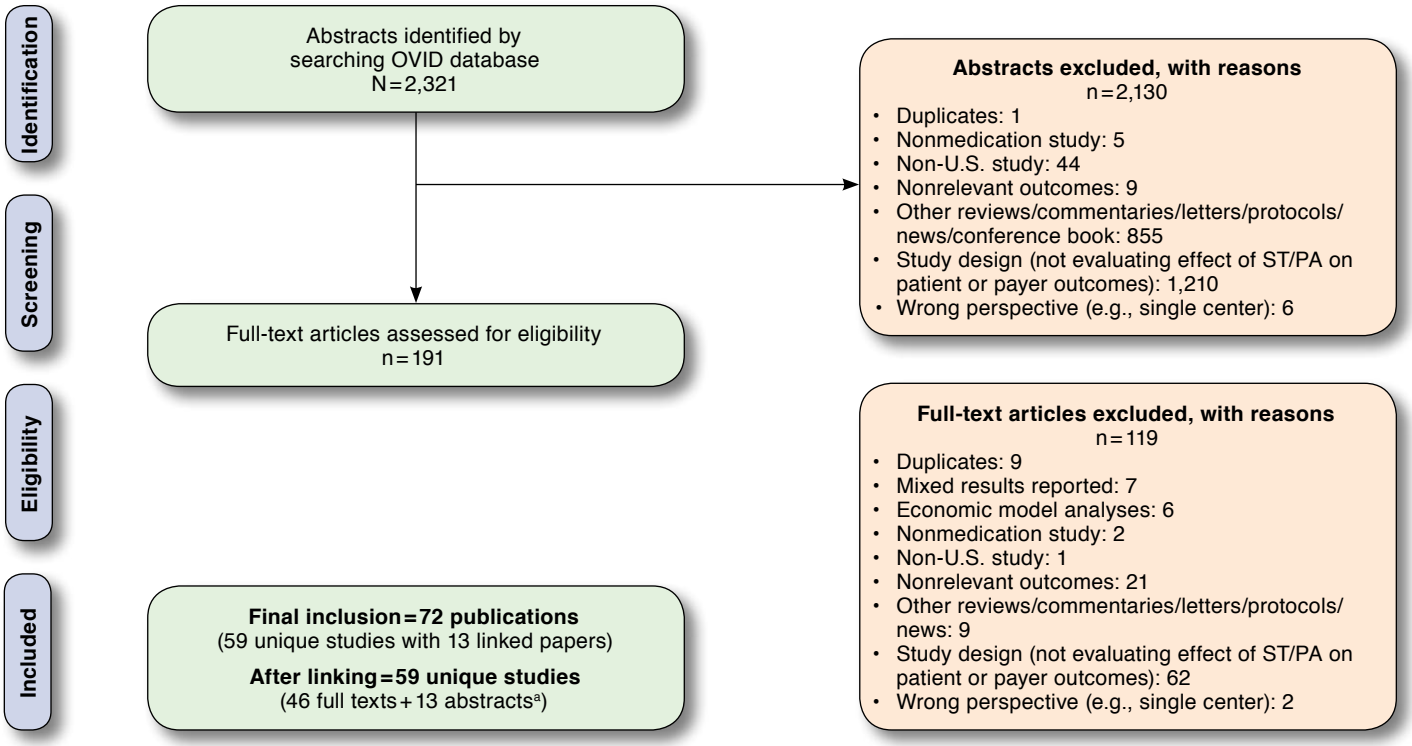
Search Strategy

This SLR was conducted using the OVID platform in the following databases: Embase (1996-February 23, 2017); MEDLINE without revisions (1996-February 23, 2017); MEDLINE in-process and other nonindexed citations (February 23, 2017); EBM Reviews—Cochrane Database of Systematic Reviews (2005-February 22, 2017); EBM Reviews—Cochrane Central Register of Controlled Trials (January 2017); and EBM Reviews—NHS Economic Evaluation Database (first quarter 2017). The search strategy comprised 2 sets of terms: (1) formulary restriction and (2) patient and payer outcomes. Seventeen formulary restriction terms (e.g., *step therap*, prior authoriz*, step edit*, fail-first, utilization manag**) and 55 outcome terms (e.g., *healthcare utiliz*, economic outcome*, inpatient*, readmission*, emergency room visit*, adherence, discontinu*, effic*, safety, adverse event*,* and *patient outcome**) were combined. The search was limited to English-language articles published from 2005 onward. Duplicates of citations (due to overlap in the coverage of the databases) were excluded. Manual searches of bibliographies of relevant systematic review articles were also performed to identify all potentially relevant articles.

Study Selection

Studies reporting the effect of PA and/or ST on patient outcomes (medication adherence, clinical outcomes, and treatment satisfaction) and payer outcomes (health care resource utilization and economic outcomes) with or without drug utilization outcomes, irrespective of disease area, were included. Reviews, letters, commentaries, economic modeling studies, studies with mixed results from different formulary restrictions, and studies only assessing the effect of formulary restrictions on drug utilization without any other outcome of interest were excluded. The outcomes assessed were medication adherence, including persistence, adherence, compliance, and discontinuation; clinical outcomes, including effectiveness and adverse events;

FIGURE 1 Study Selection Process



[a]*Conference abstracts were identified as part of OVID searches; manual searching for conference abstracts was not undertaken.*
PA=prior authorization; ST=step therapy.

patient-reported outcomes, including treatment satisfaction, treatment preference, and quality of life; health care resource utilization, including outpatient visits, hospitalizations, and ER visits; economic outcomes, including medical costs, pharmacy costs, and total costs; and drug utilization data, whenever reported along with patient- or payer-related outcomes.

All of the studies retrieved from the literature search were screened by 2 independent reviewers based on the title and abstract supplied with each citation. Any discrepancy between the reviewers was resolved through a third independent reviewer. The inclusion/exclusion criteria were uniformly applied across all studies. Studies that did not meet the eligibility criteria were excluded, and the reasons for exclusion were documented. Similar to the screening of articles based on title and abstract, full-text articles were screened, and subsequently studies that met the eligibility criteria were subjected to data extraction.

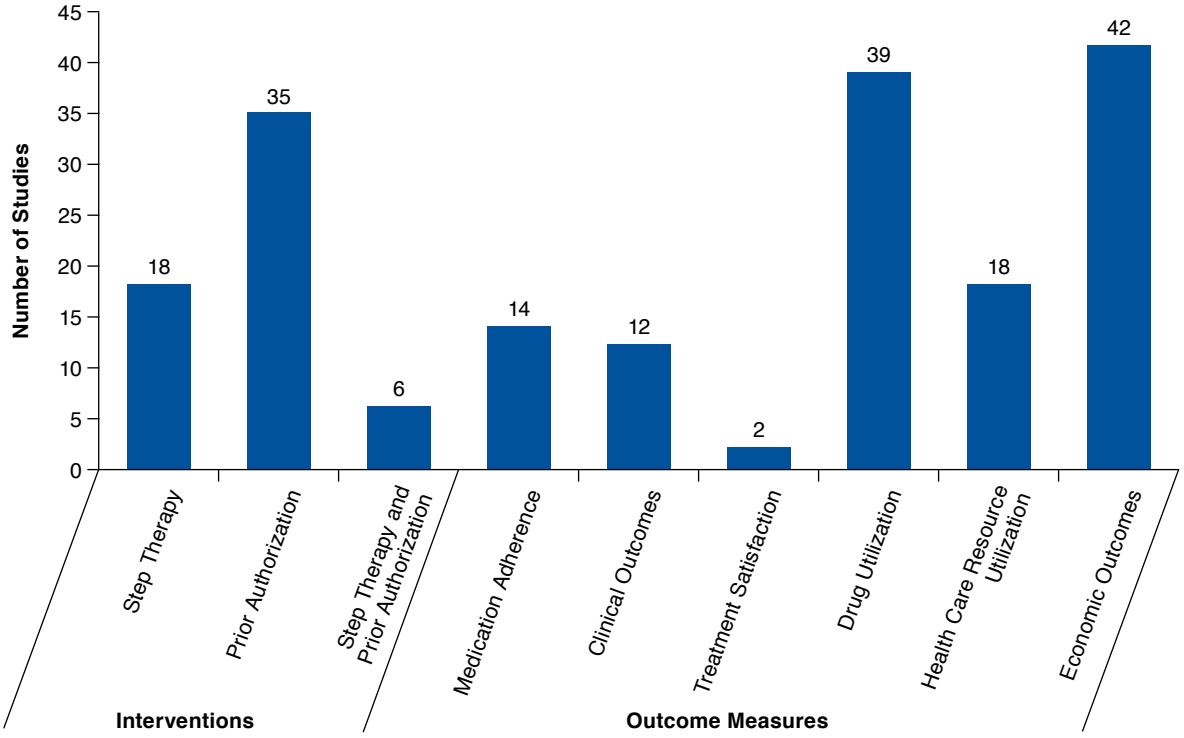
Studies with multiple publications were linked to one another and extracted as a single study. Data extraction of the included studies was performed by 1 reviewer, and the quality of the data was checked by the second reviewer, with reconciliation of any differences through a third independent reviewer.

Studies showing improvement in outcomes because of formulary restrictions were considered positive (from a patient perspective [e.g., improved adherence, persistence, efficacy, and safety] and from a payer perspective [e.g., lower health care resource utilization and costs]). Studies showing worsening of patient or payer outcomes were considered negative (from a patient perspective [e.g., worsened adherence, persistence, efficacy, and safety] or a payer perspective [e.g., higher health care resource utilization and costs]). Positive or negative association of an outcome was further categorized based on its statistical significance. Finally, if there was no effect on the previously mentioned outcomes, those outcomes were considered neutral.

Quality Assessment

Each included full-text article was assessed for methodological quality. Studies that met the eligibility criteria for the review were critically appraised for quality based on their study designs, using the Cochrane risk of bias tool for randomized controlled trials (RCTs), the Newcastle-Ottawa Scale for cohort and case-control studies, the Effective Practice and Organisation of Care risk of bias criteria for interrupted time-series studies, and the Critical Appraisal Skills Programme checklist for cross-sectional studies.[27-30]

FIGURE 2 Distribution of Studies by Type of Intervention and Patient and Payer Outcome Measures



Results

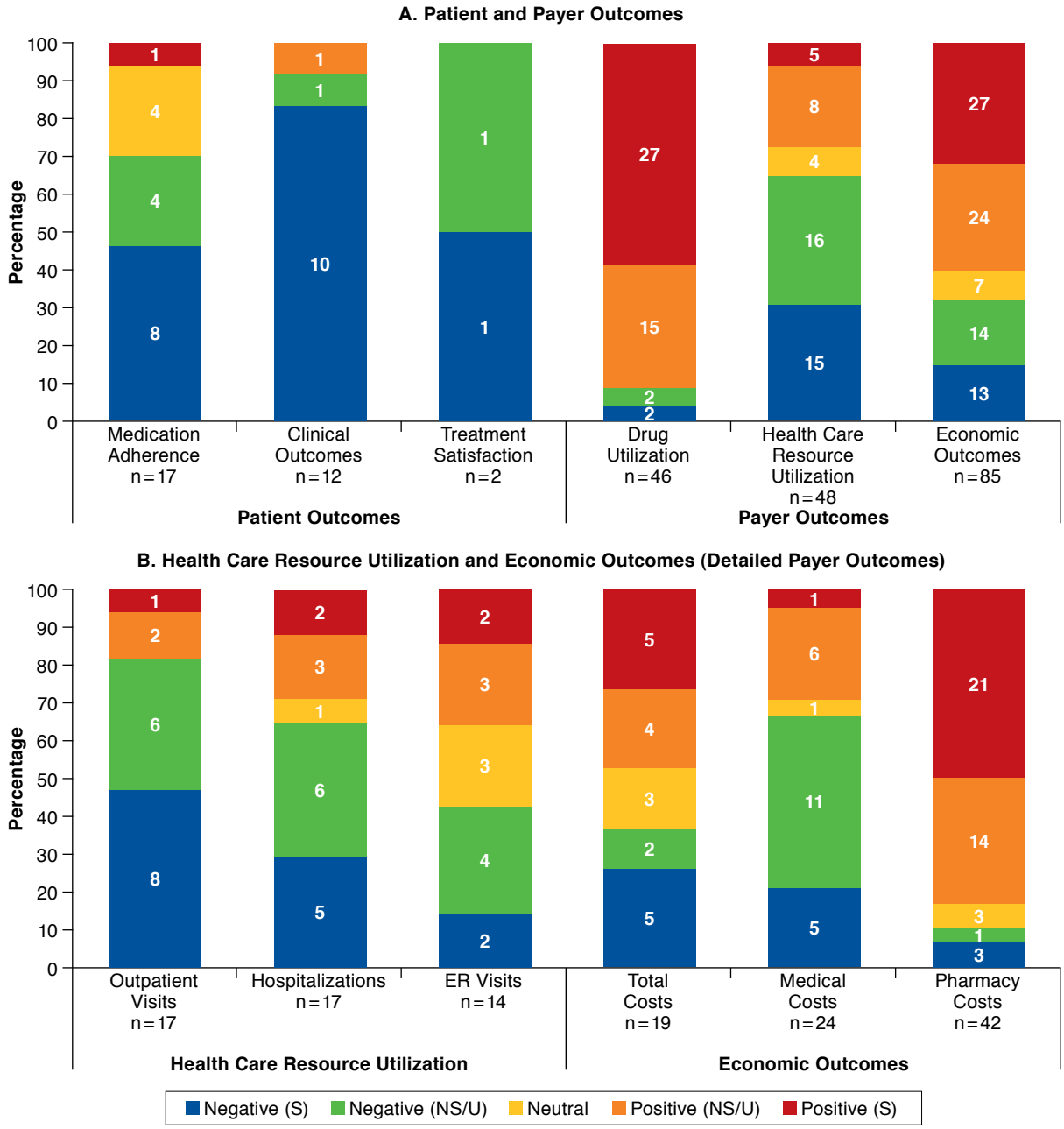
The literature search yielded 2,321 publications and resulted in the inclusion of 59 unique studies (Figure 1).[10,19-24,31-82] In total, 48 retrospective observational studies, 5 time-series analysis studies, 3 cross-sectional studies, 1 case-control study, 1 controlled before-after study, and 1 RCT were included (Appendix A, available in online article). The majority of the included studies evaluated the PA restriction, followed by the ST restriction, or both of the restrictions (Figure 2). The most frequently reported outcome in the included studies was economic outcomes, followed by drug use, health care resource utilization, medication adherence, clinical outcome, and treatment satisfaction (Figure 2).

From all of the studies published as full text that were assessed for quality assessment, the quality score for retrospective observational studies ranged from 3 to 7 stars on the Newcastle-Ottawa Scale (Appendix B, available in online article),[28] whereas assessment of time-series studies using the Effective Practice and Organisation of Care criteria yielded a "low risk" on the majority of the questions for all 5 of the studies.[29] Two of the cross-sectional studies reported clear information as per the Critical Appraisal Skills Programme criteria.[30] Only 1 RCT reported overall unclear risk of bias according to the Cochrane risk of bias tool.[27]

The 59 studies measured 164 outcomes across the patient, health care resource utilization, and economic outcome categories, as well as 46 outcomes for drug use. Of the total number of patient, health care resource utilization, and economic outcomes (n = 164), 50.6% were negative in direction or were unfavorable (n = 83); 40.2% were positive in direction or were favorable (n = 66); and 9.1% were neutral (n = 15). Across all of the negative outcomes (n = 83), statistical significance was reported in more than half of the studies (n = 47, 56.6%); statistical significance was reported in half of the studies for all of the positive outcomes (n = 33, 50%). On the other hand, for drug utilization outcomes (n = 46), more than 90% of the outcomes were positively associated with formulary restrictions (n = 42), and less than 10% were negatively associated (n = 4; Figure 3A).

Of all of the outcome types, the majority were negatively associated with formulary restrictions (medication adherence [70.6%], clinical outcome [91.7%], patient-reported outcomes [treatment satisfaction, 100%], health care resource utilization [outpatient visits, 82.4%, and hospitalization, 64.7%], and economic outcomes [medical costs, 66.6%]). However, for pharmacy costs under economic outcomes and drug utilization, 83.3% and 91.3% of outcomes reported positive association with formulary restrictions compared with negative or neutral association, respectively. A subset of studies (n = 20) that

FIGURE 3 Directional Effect of Formulary Restrictions



ER = emergency room; NS = statistically not significant; S = statistically significant; U = unclear.

included total or medical costs (in addition to pharmacy costs) was evaluated to understand the overall effect of formulary restrictions. Of the 20 studies, only 4 showed reductions in pharmacy and total costs, whereas 10 studies showed reductions in pharmacy costs with negative medical and/or total costs (n = 9) or neutral total costs (n = 1), and 7 studies showed increases or no changes in pharmacy costs (Ben-Joseph et al. [2014] was counted twice because the results differed in commercial vs. Medicare populations[36]). Outcomes such as total costs and ER visits seemed to have almost equal distribution

between positive and negative associations with formulary restrictions (Figure 3B).

Cost was the main reason for applying formulary restrictions in the majority of the included studies (n = 48), followed by multifactorial reasons (e.g., clinical/safety, n = 12). The included studies assessed patients with a variety of indications, such as diabetic peripheral neuropathy/postherpetic neuralgia/fibromyalgia/pain management (n = 12), schizophrenia/bipolar disorder (n = 9), anxiety/depression (n = 6), type 2 diabetes (n = 4), cancer (n = 3), allergic rhinitis/asthma (n = 2), and hypertension (n = 3), among others.

Plan types in the included studies were national or state Medicaid/Medicare (n = 28), commercial/employer (n = 21), Medicare/commercial (n = 2), and others (n = 9). Of all of the patient, health care resource utilization, and economic outcomes from studies assessing commercial/employer plans (n = 68), half were negatively associated with formulary restrictions (n = 34, 50%), followed by positive (n = 29, 42.6%) and neutral associations (n = 5, 7.4%). Similarly, for outcomes in Medicaid plans (n = 52), the majority was negatively associated with formulary restrictions (n = 28, 53.8%), followed by positive (n = 19, 36.6%) and neutral associations (n = 5, 9.6%). However, for outcomes in Medicare plans (n = 27), the majority was positively associated with formulary restrictions (n = 14, 51.9%), followed by negative (n = 9, 33.3%) and neutral associations (n = 4, 14.8%). Furthermore, drug utilization outcomes showed a similar trend within different managed care plans (commercial/employer: positive 92%, negative 8%; Medicare: positive 93%, negative 7%; and Medicaid: positive 88%, negative 12%).

Discussion

This SLR examined the association between formulary restrictions (specifically PA and ST) and a comprehensive list of patient and payer outcomes (medication adherence, clinical outcomes, treatment satisfaction, drug utilization, health care resource utilization, and economic outcomes) and captured their intended, as well as unintended, consequences. Our approach differed from that of previous reviews because we focused on PA and ST as the formulary restrictions, whereas previous reviews assessed cost sharing,[14,15] tiered formulary and copayment,[16] and multiple restrictions (ST, cost sharing, PA, PDLs, and quantity limits).[26]

In this SLR, a robust search strategy was used based on the Cochrane collaboration guide for SLRs,[27] whereby multiple databases were queried, including MEDLINE, Embase, and Cochrane. Previous SLRs searched only the PubMed or Embase databases.[14-16,26] Our focus was to identify recent studies (2005 onward) that looked at the effect of PA and ST because these are commonly used managed care policies that have not been systematically assessed in previous literature reviews for a wide range of patient and payer outcomes. Previous literature reviews have qualitatively summarized the evidence on the effects of formulary restrictions; however, most reviews did not carry out any directional outcome-level analysis.[14-17]

Only 1 recent SLR (Happe et al. [2014]) reported aggregated directional effect of formulary restrictions on patient and payer outcomes (i.e., medication adherence, clinical outcomes, economic outcomes, or health care resource utilization).[26] In the Happe et al. study, formulary restrictions were most frequently associated with negative outcomes (49.6%), followed by neutral (36.3%) and positive outcomes (14.1%).[26] Although we also found that formulary restrictions were most frequently associated with negative outcomes (50.6%), we observed considerably more positive outcomes (40.2%) and fewer neutral outcomes (9.1%) compared with the Happe et al. study. In addition, Happe et al. found that medication adherence had the highest proportion of negative association with the formulary restrictions (68.3%), followed by health care resource utilization (37.5%), clinical outcomes (36.4%), and economic outcomes (28.8%).[26] Our findings showed a similar proportion of studies with negative association between medication adherence and formulary restrictions (71%) but much higher negative associations between formulary restrictions and clinical outcomes (92%), health care resource utilization (64.5%), and treatment satisfaction (100%).

In agreement with the original intent, we found that formulary restrictions had a mostly positive effect on pharmacy costs. However, when the subset of studies that included total or medical costs (in addition to pharmacy costs) was evaluated, we observed that the majority of these studies showed either negative effect on total, medical, or pharmacy costs or no effect on pharmacy costs. These findings highlight the importance of evaluating more than just pharmacy costs to better understand the overall effect of formulary restrictions and hint at potential unintended consequences of formulary restrictions on payers. Moreover, we observed that results could depend on what type of payer (commercial vs. Medicare), disease state, or drug class is studied; thus, we suggest accounting for these variables when making formulary decisions.

Limitations

Certain limitations are inherent in nonrandomized studies and data, including accuracy and completeness of retrospective data, lack of control and selection, and inability to draw conclusions regarding cause and effect. The ability to draw conclusions from the reviewed studies may be impeded by differences in study design and variables included in each study. Some examples of variations observed in this literature review are study design (observational, time series, and cross-sectional); study method (difference in differences and regression); health insurance plan type (commercial, employer sponsored, Medicaid/Medicare, and TRICARE); cost type (total costs, medical costs, pharmacy

costs, and disease-specific costs); disease state; medication class; and data source. Furthermore, the outcomes assessed were defined and measured in different ways across studies. For example, medication adherence could have been measured by proportion of days covered, medication possession ratio, or number of months in which a prescription was written. In addition, we only included studies that assessed the effect of placing formulary restrictions and did not include studies that assessed the effect of removing formulary restrictions.

Studies reporting drug utilization data along with patient-related outcomes were included; however, studies reporting only pharmacy utilization data were not included as part of this SLR to maintain the scope of this review. Moreover, this systematic review focused on evaluating the effect of ST and PA and did not evaluate the effect of other formulary restrictions, such as cost sharing, PDLs, and quantity limits. Finally, this study was based on directional association of outcomes, as either positive or negative, which in some cases may be open to different interpretations (e.g., increased number of outpatient visits for chronic disease monitoring may be considered positive in some cases).

Conclusions

Findings from this SLR suggest that formulary coverage decisions by MCOs may lead to unintended consequences on patient or payer outcomes. Although formulary restrictions reduce drug utilization and associated drug costs, resulting in pharmacy cost savings, some of these cost savings may be offset by increased health care resource utilization and medical costs. Therefore, we recommend careful evaluation of formulary restriction policies before implementation and continued reevaluation while accounting for various disease states and plan types. Further research is warranted to evaluate the overall effect of formulary restrictions on patients, payers, and providers using medical and pharmacy data, in addition to understanding all related, including unseen, administrative costs.

Authors

YUJIN PARK, PharmD, and JOHN KO, PharmD, MS, Novartis Pharmaceuticals, East Hanover, New Jersey. SYED RAZA, MS; ANEESH GEORGE, MS; and RUMJHUM AGRAWAL, MPharm, Novartis Healthcare, Hyderabad, India.

AUTHOR CORRESPONDENCE: Yujin Park, PharmD, U.S. Health Economics and Outcomes Research, Novartis Pharmaceuticals, 1 Health Plaza, East Hanover, NJ 07936. Tel.: 862.325.3935; E-mail: jina.park@novartis.com.

DISCLOSURES

This study was funded by Novartis Pharmaceuticals. Park and Ko are employed by Novartis Pharmaceuticals in East Hanover, New Jersey, and Ko holds stock in Novartis. Raza, George, and Agrawal are employed by Novartis Healthcare in Hyderabad, India.

Study concept and design were contributed primarily by Park and Ko, along with the other authors. Raza, George, and Agrawal collected the data, along with Park and Ko. Data interpretation was performed by Agrawal, Raza, George, Park, and Ko. The manuscript was written and revised by Raza, George, and Park, along with Ko and Agrawal.

Results from this systematic literature review were presented at the AMCP Annual Meeting 2016; San Francisco, California; April 19-22, 2016.

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APPENDIX A Study Characteristics

Reference	Restriction Type	Indication	Study Design	Outcome Type	Outcome	Direction of Association
Margolis et al. 2010[62]	PA	Painful diabetic peripheral neuropathy or postherpetic neuralgia	Retrospective observational	Economic	1. Total costs 2. Pharmacy costs	1. Positive (NS) 2. Positive (NS)
				Utilization	1. Drug utilization	1. Positive (S)
Margolis et al. 2009[61]	PA	Diabetic peripheral neuropathy or postherpetic neuralgia	Retrospective observational	Economic	1. Total costs 2. Pharmacy costs	1. Negative (S) 2. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Devine et al. 2009[40]	PA	Gastrointestinal-related diagnoses	Retrospective observational	Adherence	1. Medication adherence	1. Negative (S)
Sun et al. 2008[74]	PA	Rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, psoriasis, and other spondyloarthropathies	Retrospective case control	Economic	1. Pharmacy costs	1. Positive (NS)
				Utilization	1. Drug utilization	1. Positive (NS)
Johnston et al. 2014[23]	PA	Painful diabetic peripheral neuropathy or fibromyalgia	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
				Utilization	1. Drug utilization	1. Positive (S)
Simeone et al. 2010[69]	PA	Multiple indications	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
				HCRU	1. Hospitalizations	1. Positive (S)
				Utilization	1. Drug utilization	1. Negative (S)
Risser et al. 2005[63]	PA	Weight loss	Retrospective observational	Adherence	1. Medication adherence	1. Positive (S)
				Clinical	1. Clinical outcomes	1. Positive (NS)
				HCRU	1. Outpatient visits	1. Negative (S)
				Utilization	1. Drug utilization	1. Negative (S)
Carroll et al. 2006[38]	PA	Gastrointestinal related or pain	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Accurso 2015[31]	PA	Opioid dependence	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
Garcia et al. 2014[48]	PA	Pain management	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Placzek et al. 2015[66]	PA	Painful diabetic peripheral neuropathy or fibromyalgia	Retrospective observational	Adherence	1. Medication adherence	1. Neutral
				Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Negative (NS) 2. Negative (NS) 3. Neutral
				Utilization	1. Drug utilization	1. Positive (NS)
Goldman et al. 2014[47]	PA	Schizophrenia	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
Starner et al. 2014[22]	PA	Bacterial pneumonia, skin and skin structure infections, and vancomycin-resistant enterococcal infections	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Positive (S) 2. Positive (NS) 3. Positive (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (NS) 2. Positive (NS) 3. Negative (NS)
				Utilization	1. Drug utilization	1. Positive (S)
Gleason et al. 2013[49]	PA	Multiple sclerosis	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (S)
Whiteley et al. 2011[82]	PA	Major depressive disorder	Retrospective observational	HCRU	1. Outpatient visits 2. Hospitalizations	1. Negative (S) 2. Negative (S)
				Utilization	1. Drug utilization	1. Positive (S)
Starner et al. 2012[10]	PA	Type 2 diabetes	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Prescription	1. Positive (S)
Law et al. 2010[59]	PA	Hypertension	Time-series analysis	Economic	1. Pharmacy costs	1. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)

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APPENDIX A Study Characteristics *(continued)*

Reference	Restriction Type	Indication	Study Design	Outcome Type	Outcome	Direction of Association
Walthour et al. 2010[79]	PA	Schizophrenia	Retrospective observational	HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Positive (NS) 2. Positive (S) 3. Positive (S)
Erdman et al. 2010[43]	PA	Breast cancer	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (U)
Siracuse et al. 2008[70]	PA	Pain management	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (S)
Hartung et al. 2006[46]	PA	Multiple diseases	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
Lu 2011[55]	PA	Hyperlipidemia	Time-series analysis	Economic	1. Pharmacy costs	1. Positive (NS)
				Utilization	1. Drug utilization	1. Positive (NS)
Lu 2011[54]	PA	Bipolar disorder	Retrospective observational	Adherence	1. Medication adherence	1. Negative (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (NS) 2. Negative (NS) 3. Positive (NS)
Seabury et al. 2014[67,a]	PA	Major depressive disorder	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Neutral 2. Negative (NS) 3. Neutral
				HCRU	1. Hospitalizations	1. Negative (S)
Keast et al. 2014[51]	PA	Allergic rhinitis, asthma, or both	Retrospective observational	HCRU	1. Outpatient visits 2. Emergency room visits	1. Positive (S) 2. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Delate et al. 2005[35]	PA	Gastrointestinal-related diagnoses	Time-series analysis	Economic	1. Medical costs 2. Pharmacy costs	1. Negative (U) 2. Positive (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (S) 2. Negative (S) 3. Negative (S)
				Utilization	1. Drug utilization	1. Positive (S)
Clark et al. 2014[24]	PA	Opioid dependence	Retrospective observational	Adherence	1. Medication adherence	1. Negative (NS)
				Clinical	1. Clinical outcomes	1. Negative (S)
				Economic	1. Total costs 2. Pharmacy costs	1. Negative (S) 2. Positive (S)
				Utilization	1. Drug utilization	1. Positive (NS)
Adams et al. 2009[37]	PA	Depression	Retrospective observational	Adherence	1. Medication adherence	1. Negative (NS)
				HCRU	1. Hospitalizations 2. Emergency room visits	1. Negative (NS) 2. Neutral
				Utilization	1. Drug utilization	1. Positive (S)
Zhang et al. 2009[78]	PA	Bipolar disorder	Retrospective observational	Adherence	1. Medication adherence	1. Negative (S)
				Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (S)
Gleason et al. 2005[39]	PA	Inflammation/pain management	Retrospective observational	Economic	1. Medical costs 2. Pharmacy costs	1. Negative (S) 2. Positive (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Positive (NS) 2. Negative (NS) 3. Negative (NS)
				Utilization	1. Drug utilization	1. Positive (S)
Soumerai et al. 2008[71]	PA	Schizophrenia	Retrospective observational	Adherence	1. Medication adherence	1. Negative (NS)
				Economic	1. Pharmacy costs	1. Positive (S)
				Utilization	1. Drug utilization	1. Positive (NS)

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APPENDIX A Study Characteristics *(continued)*

Reference	Restriction Type	Indication	Study Design	Outcome Type	Outcome	Direction of Association
Ben-Joseph et al. 2014[36]	PA (Commercial)	Pain management	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Negative (S) 2. Negative (S) 3. Negative (S)
				HCRU	1. Outpatient visits	1. Negative (S)
				Utilization	1. Drug utilization	1. Positive (NS)
	PA (Medicare)	Pain management		Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Negative (S) 2. Negative (S) 3. Positive (NS)
				HCRU	1. Outpatient visits	1. Negative (S)
				Utilization	1. Drug utilization	1. Positive (NS)
Brown et al. 2013[34]	PA	Schizophrenia and bipolar disorder	Retrospective observational	Adherence	1. Medication adherence	1. Negative (S)
Herink et al. 2015[52]	PA	Patients with a claim for anticoagulants	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (U)
				Utilization	1. Drug utilization	1. Positive (U)
Step Therapy						
Mark et al. 2010[19]	ST	Depression	Retrospective observational	Adherence	1. Medication adherence	1. Neutral
				Economic	1. Medical costs 2. Pharmacy costs	1. Negative (U) 2. Positive (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (S) 2. Negative (S) 3. Negative (S)
				Utilization	1. Drug utilization	1. Positive (NS)
Mark et al. 2009[21]	ST	Hypertension	Retrospective observational	Adherence	1. Medication adherence	1. Negative (S)
				Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Positive (S) 2. Negative (NS) 3. Positive (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (S) 2. Negative (S) 3. Positive (NS)
				Utilization	1. Drug utilization	1. Positive (S)
Sun et al. 2007[75]	ST	Allergic rhinitis	Retrospective observational	Economic	1. Total costs	1. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Yokoyama et al. 2007[77]	ST	Hypertension	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
Dunn et al. 2006[44]	ST	Depression	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Hatoum et al. 2011[50]	ST	Lymphoma	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
Williams et al. 2012[20]	ST	Type 2 diabetes	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
				Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Negative (U) 2. Negative (U) 3. Negative (U)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (U) 2. Negative (U) 3. Negative (U)
Udall et al. 2013[80]	ST	Painful diabetic peripheral neuropathy, postherpetic neuralgia, or fibromyalgia	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Negative (S) 2. Negative (NS) 3. Positive (NS)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (S) 2. Positive (NS) 3. Negative (NS)
				Utilization	1. Drug utilization	1. Positive (NS)

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APPENDIX A Study Characteristics *(continued)*

Reference	Restriction Type	Indication	Study Design	Outcome Type	Outcome	Direction of Association
Suehs et al. 2014[68]	ST	Painful diabetic peripheral neuropathy, postherpetic neuralgia, or fibromyalgia	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Positive (NS) 2. Positive (NS) 3. Negative (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (NS) 2. Positive (NS) 3. Neutral
				Utilization	1. Drug utilization	1. Positive (S)
Tunis et al. 2006[73]	ST	Schizophrenia	Randomized controlled trial	Clinical	1. Clinical outcomes	1. Negative (S)
				Economic	1. Total costs 2. Pharmacy costs	1. Neutral 2. Positive (S)
Zhang et al. 2012[81]	ST	Epilepsy	Retrospective observational	Economic	1. Medical costs 2. Pharmacy costs	1. Negative (NS) 2. Positive (S)
				HCRU	1. Outpatient visits 2. Hospitalizations 3. Emergency room visits	1. Negative (NS) 2. Neutral 3. Neutral
Blomquist et al. 2010[32]	ST	Gastrointestinal-related diagnoses	Retrospective controlled before-after	Economic	1. Pharmacy costs	1. Positive (S)
Null et al. 2016[64]	ST (Medicare Advantage)	Painful diabetic peripheral neuropathy or postherpetic neuralgia or fibromyalgia	Time-series analysis	Economic	1. Total costs 2. Medical costs	1. Positive (S) 2. Neutral
				Utilization	1. Drug utilization	1. Positive (NS)
	ST (Commercial)			Economic	1. Total costs 2. Medical costs	1. Positive (NS) 2. Positive (NS)
				Utilization	1. Drug utilization	1. Positive (S)
Cotter et al. 2011[41]	ST	Type 2 diabetes	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (S)
Lin et al. 2012[58]	ST	Breast and lung cancer	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
Suehs et al. 2015[72]	ST	Attention deficit/hyperactivity disorder	Retrospective observational	Adherence	1. Medication adherence	1. Negative (S)
				Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Positive (S) 2. Positive (NS) 3. Positive (S)
				Utilization	1. Drug utilization	1. Positive (S)
Harman et al. 2016[45]	ST	Rheumatoid arthritis/multiple sclerosis	Retrospective observational	Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (U)
Effect of Step Therapy/Prior Authorization						
Louder et al. 2011[57]	ST/PA	Osteoarthritis or rheumatoid arthritis	Retrospective observational	Clinical	1. Clinical outcomes	1. Negative (S)
				Economic	1. Medical costs	1. Negative (S)
				Utilization	1. Drug utilization	1. Positive (S)
West et al. 2010[76]	ST/PA	Psychiatric patients	Cross sectional	Clinical	1. Clinical outcomes	1. Negative (S)
				Utilization	1. Drug utilization	1. Positive (S)
Nau et al. 2007[65]	ST/PA	NR	Cross sectional	PROs	1. Difficulties related to PA or ST	1. Negative (U)
Farley et al. 2008[42]	ST/PA	Overall cohort and schizophrenia subgroup	Time-series analysis	Economic	1. Medical costs 2. Pharmacy costs	1. Negative (U) 2. Positive (S)
				Utilization	1. Drug utilization	1. Negative (NS)
Seabury et al. 2014[67,a]	ST/PA	Major depressive disorder	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Neutral 2. Negative (S) 3. Neutral
				HCRU	1. Hospitalizations	1. Negative (NS)

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APPENDIX A Study Characteristics *(continued)*

Reference	Restriction Type	Indication	Study Design	Outcome Type	Outcome	Direction of Association
Shen et al. 2016[60]	ST/PA	Low-income subsidized users of oral hypoglycemic agents	Retrospective observational	Adherence	1. Medication adherence	1. Neutral
				Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (U)
		Low-income subsidized users of statins		Adherence	1. Medication adherence	1. Neutral
				Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (U)
		Low-income subsidized users of renin-angiotensin system antagonists		Adherence	1. Medication adherence	1. Negative (U)
				Economic	1. Pharmacy costs	1. Positive (U)
				Utilization	1. Drug utilization	1. Positive (U)
Effect of Restrictions on No Claims vs. Approved Claims						
Bergeson et al. 2013[33]	PA	Type 2 diabetes	Retrospective observational	Economic	1. Total costs 2. Medical costs 3. Pharmacy costs	1. Positive (NS) 2. Positive (NS) 3. Negative (S)
Effect of Restrictions on Different Disease States						
Johnston et al. 2012[53]	PA	Painful diabetic peripheral neuropathy or postherpetic neuralgia	Retrospective observational	Economic	1. Medical costs	1. Positive (S)
	ST			Economic	1. Medical costs	1. Negative (NS)
	PA	Fibromyalgia		Economic	1. Medical costs	1. Positive (NS)
	ST			Economic	1. Medical costs	1. Negative (NS)
	PA	Painful diabetic peripheral neuropathy or postherpetic neuralgia		Utilization	1. Drug utilization	1. Positive (S)
	ST			Utilization	1. Drug utilization	1. Negative (NS)
	PA	Fibromyalgia		Utilization	1. Drug utilization	1. Positive (S)
	ST			Utilization	1. Drug utilization	1. Positive (S)
LaPensee et al. 2010[56]	ST	Anxiety/depression	Cross-sectional	Adherence	1. Medication adherence	1. Negative (S)
				PROs	1. Patient satisfaction	1. Negative (S)

[a]*Seabury et al. (2014) reported 2 groups: 1 group was exposed to PA restriction and the other group was exposed to PA and ST restrictions.*

HCRU = health care resource utilization; NR = not reported; NS = not significant; PA = prior authorization; PRO = patient-reported outcome; S = significant; ST = step therapy; U = unclear.

APPENDIX B Quality Assessment of Nonrandomized Studies by Newcastle-Ottawa Scale

Author	Selection				Comparability	Exposure			Number of Stars
Cohort studies	1	2	3	4		1	2	3	
Lu et al. 2011[55]	★	★	★	☆	★★	★	★	☆	★★★★★★★
Margolis et al. 2010[62]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Mark et al. 2010[19]	★	☆	★	☆	★☆	★	★	☆	★★★★★
Walthour et al. 2010[79]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Margolis et al. 2009[61]	★	☆	★	☆	★★	★	★	★	★★★★★★★
Adams et al. 2009[37]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Zhang et al. 2009[78]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Mark et al. 2009[21]	★	★	★	☆	★★	★	★	☆	★★★★★★★
Soumerai et al. 2008[71]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Siracuse et al. 2008[70]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Sun et al. 2007[75]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Yokoyama et al. 2007[77]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Hartung et al. 2006[46]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Dunn et al. 2006[44]	★	★	★	☆	☆☆	★	★	☆	★★★★★
Carroll et al. 2006[38]	★	☆	★	☆	★★	☆	★	☆	★★★★★
Risser et al. 2005[63]	★	★	★	☆	★☆	★	★	☆	★★★★★★
Gleason et al. 2005[39]	★	★	★	☆	☆☆	★	★	☆	★★★★★
Simeone et al. 2010[69]	★	★	★	☆	☆☆	★	★	☆	★★★★★
Louder et al. 2011[57]	★	☆	★	☆	★☆	★	★	☆	★★★★★
Suehs et al. 2015[72]	★	☆	★	☆	★☆	★	★	☆	★★★★★
Johnston et al. 2014[23]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Garcia et al. 2014[48]	★	★	★	☆	☆☆	★	☆	☆	★★★★
Clark et al. 2014[24]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Suehs et al. 2014[68]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Placzek et al. 2015[66]	★	★	★	☆	★★	★	★	☆	★★★★★★★
Ben-Joseph et al. 2014[36]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Goldman et al. 2014[47]	☆	★	★	☆	★★	★	☆	☆	★★★★★
Keast et al. 2014[51]	★	☆	★	☆	☆☆	★	☆	☆	★★★
Starner et al. 2014[22]	★	☆	★	☆	★★	★	☆	☆	★★★★★
Lin et al. 2012[58]	★	★	★	☆	★★	★	★	☆	★★★★★★★
Brown et al. 2013[34]	★	☆	★	☆	★★	★	☆	☆	★★★★★
Bergeson et al. 2013[33]	★	☆	★	☆	★★	★	★	★	★★★★★★★
Udall et al. 2013[80]	★	☆	★	☆	★★	★	★	☆	★★★★★★
Gleason et al. 2013[49]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Williams et al. 2012[20]	★	★	★	☆	☆☆	★	★	☆	★★★★★
Starner et al. 2012[10]	★	☆	★	☆	☆☆	★	★	☆	★★★★
Harman et al. 2016[45]	★	★	★	☆	☆☆	★	☆	☆	★★★★
Case-control study									
Sun et al. 2008[74]	★	★	★	★	☆☆	★	★	☆	★★★★★★

Note: A study can be awarded a maximum of 1 star for each numbered item within the Selection and Exposure categories. A maximum of 2 stars can be given for Comparability. A higher number of total stars depicts better quality for the study.