Effect of 6 Managed Care Pharmacy Tools:
A Review of the Literature

Abt Associates, Inc., for the Academy of Managed Care Pharmacy
To the reader:

In late 2009, the Academy of Managed Care Pharmacy contracted with Abt Associates on an initiative which was designed to identify and describe managed care pharmacy tools and activities. The approach was to provide a review of the literature documenting the outcomes that managed care pharmacy produces. With this JMCP supplement, the Academy is sharing the document which includes primary sources of literature that describe the effects of 6 managed care pharmacy tools. A complete annotated bibliography and literature summary tables were also developed and are available online at: http://www.amcp.org/bibliography.pdf and http://www.amcp.org/summarytables.pdf, respectively.

The report concluded that there is strong evidence on the effectiveness of several managed care pharmacy tools for achieving intended outcomes like increased utilization of preferred drugs, formulary compliance and decreased prescription drug spending. These results support the assertion that managed care pharmacy continues to make health care more affordable for patients and payers. Abt Associates indicated that, while there is a substantial body of literature on several managed care pharmacy interventions, there are several interventions that require additional research, especially in clinical and humanistic outcomes, in order to provide decision makers with a more comprehensive understanding of the value of managed care pharmacy tools.

Two limitations should be noted in interpreting the conclusions in this report. First, the literature search was restricted to research conducted within managed care organizations. Therefore it represents only a portion of the available literature on managed care pharmacy. Second, the Academy is aware that the published literature does not represent the full array of research in the area of managed care pharmacy. Managed care organizations analyze internal data on a regular basis to make determinations about the success or appropriateness of continued use of managed care tools. Unfortunately this valuable internal research is not often made public and, therefore, is not included in this literature review.

We encourage managed care organizations both to publish studies based on analyses on existing internal data and to conduct new research in managed care pharmacy interventions that is focused on patient outcomes. This information is valuable to both health care practitioners in managed care settings and to policy makers.

Sincerely,

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AMCP Executive Director

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### Table of Contents

**Effect of 6 Managed Care Pharmacy Tools: A Review of the Literature**

*Abt Associates, Inc., for the Academy of Managed Care Pharmacy*

<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td>Executive Summary</td>
</tr>
<tr>
<td>S4</td>
<td>Introduction</td>
</tr>
<tr>
<td>S4</td>
<td>Methods</td>
</tr>
<tr>
<td>S4</td>
<td>Results</td>
</tr>
<tr>
<td>S4</td>
<td>Tiered Formularies</td>
</tr>
<tr>
<td>S6</td>
<td>Prior Authorization</td>
</tr>
<tr>
<td>S7</td>
<td>Step Therapy</td>
</tr>
<tr>
<td>S8</td>
<td>Therapeutic Interchange</td>
</tr>
<tr>
<td>S9</td>
<td>Drug Utilization Review</td>
</tr>
<tr>
<td>S10</td>
<td>Medication Therapy Management</td>
</tr>
<tr>
<td>S13</td>
<td>Discussion</td>
</tr>
<tr>
<td>S13</td>
<td>Future Research</td>
</tr>
<tr>
<td>S14</td>
<td>Limitations</td>
</tr>
<tr>
<td>S14</td>
<td>Conclusion</td>
</tr>
<tr>
<td>S17</td>
<td>References</td>
</tr>
<tr>
<td>S17</td>
<td>Appendix I: Detailed Methods</td>
</tr>
<tr>
<td>S17</td>
<td>Search Strategy</td>
</tr>
<tr>
<td>S17</td>
<td>PubMed Search</td>
</tr>
<tr>
<td>S17</td>
<td>Scan Relevant Review Articles’ Bibliographies</td>
</tr>
<tr>
<td>S17</td>
<td>Targeted Search of Relevant Journals</td>
</tr>
<tr>
<td>S17</td>
<td>Recommended Articles from Experts</td>
</tr>
<tr>
<td>S17</td>
<td>Selection Criteria</td>
</tr>
<tr>
<td>S17</td>
<td>Inclusion Criteria</td>
</tr>
<tr>
<td>S17</td>
<td>Exclusion Criteria</td>
</tr>
<tr>
<td>S18</td>
<td>Refined Selection Criteria for Specific Interventions</td>
</tr>
<tr>
<td>S19</td>
<td>Selected Articles for Review</td>
</tr>
<tr>
<td>S19</td>
<td>Reviewing the Literature</td>
</tr>
<tr>
<td>S19</td>
<td>Rating the Literature</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY

The prescription drug benefits of private and public payers are administered and managed with increasing frequency by pharmacy benefit management companies (PBMs) and managed care organizations (MCOs). In light of the passage of The Patient Protection and Affordable Care Act (PPACA) and growth in covered populations, managed care pharmacy interventions will likely be employed to administer a growing body of expanded benefits. Abt Associates conducted a review of the literature on 6 managed care pharmacy interventions that we selected in conjunction with the Academy of Managed Care Pharmacy (AMCP), including step therapy, prior authorization (PA), therapeutic interchange, tiered formularies, drug utilization review (DUR), and medication therapy management (MTM). The objectives of the review were to summarize the effects of the selected interventions based on a scan and quality rating of the literature from the past 10 years and to identify those areas in which adequate literature does not exist. We reviewed and rated a total of 62 unique articles, representing studies on tiered formularies (n = 27), PA (n = 9), step therapy (n = 7), therapeutic interchange (n = 5), DUR (n = 4), and MTM (n = 11) interventions (1 study addressed both tiered formulary and step-therapy intervention).

The tiered formulary body of literature is quite deep and rich with detailed findings that have important implications for benefit design. The 27 articles reviewed demonstrate that tiered formularies are associated with decreased drug utilization of nonpreferred drugs, encourage formulary compliance among patients, and reduce prescription drug spending. The findings with respect to patient out-of-pocket spending are mixed. Given that tiered formularies are one of the most common managed care pharmacy tools, additional research is needed to examine the effects on patient health outcomes and humanistic outcomes. Information on drug rebates should also be included in the analyses.

PA is consistently associated with reductions in utilization of and expenditures on the nonpreferred agent. The literature suggests that PA is an effective cost-management tool, but it is unclear if patients are impacted positively or negatively (e.g., mixed findings on discontinuation rates). The PA literature consistently shows significant reductions in pharmacy utilization and spending and, when studied, does not increase other medical costs. Additional research on PA is needed to expand current evidence, including analyzing patient outcomes, patient satisfaction and quality of life, and administrative costs associated with PA policy.

Step-therapy interventions are used to encourage the use of therapeutically equivalent, lower-cost medications for several different therapeutic classes. Step-therapy interventions effectively encourage the utilization of first-step drugs. A few studies found that step-therapy interventions were associated with lower continuation rates or higher discontinuation rates. Several studies found that step-therapy interventions effectively lowered the prescription drug costs of the payers. Two studies examined the effect of step-therapy interventions on medical utilization and cost with mixed results. There is a paucity of research examining the effect of step therapy on medical utilization and costs and clinical and humanistic outcomes.

The literature on therapeutic interchange examines programs for several different therapeutic drug classes as well as voluntary and mandatory programs. Therapeutic interchange programs effectively shift patients to preferred drugs, although some studies observe patients switching back to the nonpreferred drug. The findings on the effects of therapeutic interchange programs on costs and clinical outcomes are mixed. While there is little research on the effect of therapeutic interchange on clinical and humanistic outcomes, the use of therapeutic interchange as a tool has declined with the adoption of tiered benefit designs and step therapy and therefore is a low priority.

DUR interventions targeted at contraindicated or inappropriate medications appear to result in increased discontinuation rates for the target drug(s). While managed care pharmacists report widespread use of DUR as a tool, there is limited published research examining the effect of DUR as a distinct intervention in the past 10 years, and the few that are published are of low quality.

MTM programs and interventions are associated with improvements in several clinical measures including blood pressure, cholesterol levels, and Healthcare Effectiveness Data and Information Set (HEDIS) hypertension measures. A few studies examine the effect of MTM on health care utilization (e.g., hospitalization, emergency room [ER] visit) with mixed results. The effect of MTM on the number of medications (i.e., polypharmacy) and the medication costs are mixed. Additional rigorous studies of the effect of MTM on clinical and humanistic outcomes would strengthen the evidence base. Future research on the savings associated with or costs avoided by MTM should incorporate the program and administration costs (e.g., pharmacist salaries). There have been several studies of MTM in managed care settings, but there is relatively little published literature on the effect of Medicare Part D MTM despite the requirement that all Medicare Part D plans offer MTM to eligible beneficiaries since 2006.

There is strong evidence on the effectiveness of several managed care pharmacy tools for achieving intended outcomes such as increased utilization of preferred drugs, formulary compliance, and decreased prescription drug spending. While there is a substantial body of literature on several managed care pharmacy interventions, there are several interventions that require additional research, especially in clinical and humanistic outcomes, in order to provide decision makers with a more comprehensive understanding of the value of managed care pharmacy tools.
Effect of 6 Managed Care Pharmacy Tools: A Review of the Literature

Introduction
The prescription drug benefits of private and public payers, including the Medicare Part D benefit for prescription drugs implemented in 2006, are administered and managed with increasing frequency by pharmacy benefit management companies (PBMs) and other managed care organizations (MCOs).

Several managed care interventions or tools exist to help PBMs and MCOs efficiently and effectively manage prescription drug benefits, aiming to (a) contain costs, (b) influence utilization, (c) encourage appropriate and cost-effective prescribing practices, and (d) improve therapeutic outcomes and reduce adverse events. In light of the passage of The Patient Protection and Affordable Care Act (PPACA; i.e., health reform) and expected growth in covered populations, managed care pharmacy interventions will likely be employed to administer and manage the expanded benefits. Therefore, it is critical for regulators and decision makers to have the requisite evidence needed to make informed decisions about the proposed strategies to manage any expanded benefits for the U.S. population.

Towards that end, Abt Associates conducted a review of the literature on 6 managed care pharmacy interventions that we selected in conjunction with the Academy of Managed Care Pharmacy (AMCP), including: step therapy, prior authorization (PA), therapeutic interchange, tiered formularies, drug utilization review (DUR), and medication therapy management (MTM). The objectives of this review were as follows:
- To summarize the effect of 6 managed care pharmacy interventions based on a scan and rating of the relevant literature from the past 10 years
- To identify those areas in which adequate literature does not exist to provide a thorough examination of the managed care pharmacy tool
- To provide a review of the literature on selected interventions that can serve to educate stakeholders and decision makers on the value of managed care pharmacy interventions

Methods
Abt Associates conducted a review of the literature on 6 managed care pharmacy interventions that we selected in conjunction with the AMCP, including step therapy, PA, therapeutic interchange, tiered formularies, DUR, and MTM. The objectives of the review were to summarize the effects of the selected interventions based on a scan and quality rating of the literature from the past 10 years and to identify those areas in which adequate literature does not exist. We identified literature from a PubMed search, a targeted scan of managed care journals, and a scan of the bibliographies of 6 review articles on managed care pharmacy interventions. We reviewed and rated a total of 62 unique articles, representing studies on tiered formularies (n = 27), PA (n = 9), step therapy (n = 7), therapeutic interchange (n = 5), DUR (n = 4), and MTM (n = 11) interventions (1 study addressed both tiered formulary and step-therapy intervention). As Table 1 illustrates, nearly a third of the articles were rated “good,” over half (57%) received a “fair” rating, and the remaining 11% were rated “poor.” The distribution of quality ratings varied across interventions. For example, neither therapeutic interchange nor DUR had any “good” quality articles, whereas at least 40% of tier and PA articles were rated as “good.” A detailed description of the rating scale and methods are provided in the Appendix.

Results
We reviewed 62 unique articles representing 7 step-therapy studies, 9 PA studies, 27 tiered formulary studies, 5 therapeutic interchange studies, 4 DUR studies, and 11 MTM studies (1 study addressed both a tiered formulary and step-therapy intervention). We present the results of the review for each of the 6 interventions, as well as outline areas in which adequate research does not exist for each of the interventions.

Tiered Formularies: Summary of the Literature
- The tiered formulary body of literature is quite deep and rich with detailed findings that have important implications for benefit design.
- The 27 articles reviewed demonstrate that tiered formularies are associated with a decrease in drug utilization of nonpreferred drugs, encourage formulary compliance among patients, and reduce prescription drug spending.
- Findings with respect to patient out-of-pocket spending are mixed.
- Given that tiered formularies are one of the most common managed care pharmacy tools, additional research is needed to examine the effects on patient health outcomes and humanistic outcomes.
- Information on drug rebates should also be included in study analyses.

A prominent approach in formulary management is the use of tiered formularies. In tiered-copayment designs, members have financial incentives (lower cost share) to use nonpreferred medications over branded products or to use preferred brand drugs (typically tier-2 copayment) rather than nonpreferred brand drugs (typically tier-3 copayment). There is extensive literature evaluating the effect of tiered formularies on several broad outcome measure categories: drug utilization, formulary compliance, and spending. Most studies, with some exceptions, reviewed the same classes of drugs and often included angiotensin-converting enzyme (ACE) inhibitors, proton-pump inhibitors (PPIs), selective serotonin reuptake inhibitors (SSRIs), drugs for dyslipidemia, and diabetes medications. We identified and reviewed 27 articles on tiered formularies, and
summarize the findings from the literature by each of the 3 broad outcome categories below.

**Drug Utilization.** The literature on the effects of tiered formularies on drug utilization has typically examined specific measures such as medication possession ratio (MPR) or adherence rates, drug discontinuation, and use of new prescriptions. Several studies found a decrease in the probability of using the nonpreferred (or nongeneric) prescribed medication as the result of various tiered formulary approaches, including adoption of a tiered formulary, moving to a higher-tier system (e.g., 3 tiers from 2 tiers), higher copayments, and shifting a specific medication to a higher tier.7-11 Furthermore, variation within these formulary approaches (e.g., different increases in copayments) had differential effects on the use of generic or preferred drugs;9 this is an important distinction for decision makers to consider when changing to copayment levels. There are important exceptions to these generalized findings, however. For instance, Huskamp et al. (2003) reported that 1 of the 2 employers had a significantly lower rate of discontinuation in the intervention arm compared with the control arm,8 and Meissner et al. (2004) found no significant differences in prescription utilization per patient as a result of increased copayments within a tiered formulary.14 The effect that changing tiers has on medication adherence, as measured by the MPR, is mixed. Some studies found small to no effects,8,15 while Taira et al. (2006) found significant differences in the MPR across tiers; specifically, lower MPR rates in higher tiers.16 Using a simple pre/post design (this article received a “poor” quality rating), Mahoney (2005) found that moving from a 2- or 3-tier formulary to a 1-tier formulary with lower copayments was associated with increased medication adherence, as measured by the MPR.17

**Formulary Compliance.** Literature assessing the effect of tiered formularies on formulary compliance examined factors that influenced patients’ decisions to switch from nonformulary drugs to formulary drugs and changes from nonpreferred to preferred brands. Studies examining formulary compliance generally found that patients switched to generics or preferred brands from nonformulary or nonpreferred brands as a result of changes or differences in tiered formularies. Several studies compared multi-tiered formularies with 2-tiered or 1-tiered formularies or evaluated the effect of switching from one to the other. The studies found that this change resulted in the desired switch or utilization,11,15,18 an increased use of formulary drugs or preferred brands,13,19-25 or an increased utilization of over-the-counter drugs.26,27 These findings were robust across articles of varying quality.

**Spending.** Many studies examined the effect of tiered formularies on spending, including prescription drug spending, patient out-of-pocket spending, medical costs, and total spending.

Several studies found a decrease in the MCO’s prescription drug spending for specific drugs in multi-tiered formularies or when switched to multi-tiered formularies or, conversely, an increase in prescription drug spending with a switch from a multi-tiered formulary to a 1-tier formulary.8,10,15,17 Similarly, Joyce et al. (2002) found that spending was lower among higher cost-sharing plans compared with lower cost-sharing plans.28 Furthermore, the authors found that patient out-of-pocket (OOP) spending did not change substantially within specific benefit designs, in part because higher copayments were offset by reduced drug use.28 Conversely, other studies found that multi-tiered formularies were accompanied with an increase in OOP spending for the patient.11,22 The difference in findings for patient OOP spending is likely due, at least in part, to the different methodologies employed and varying rigor of the analysis. For studies that examined multiple drug classes, changes in spending often varied across the different drug classes examined.15,26

Studies that analyzed total spending had mixed results. Some studies did not find differences in health care costs (i.e., inpatient, outpatient, emergency room, and pharmacy costs) after a change to a multi-tiered formulary9,10 or copayment increases within tiers,8 while other studies found that multi-tiered formularies decreased or had lower total drug spending.11,22,29 Studies also examined the effect of various tiered formularies approaches on the health plan or payer spending and exhibited some variability. Fairman et al. (2003) found slower rates of increases to net insurer costs for a 3-tier formulary compared with a 2-tier formulary;17 and several authors found significant decreases in plan spending with higher copayments in second and third tiers compared with the first tier.9,22,27,29 Although considered a “poor” quality article, Berger (2007) also reported similar findings: a shift from a 3-tier to a 1-tier formulary increased the payer’s total annual pharmacy costs.30

While there is extensive literature examining the effect of several variations of tiered formularies for several different classes of drugs, there are opportunities to strengthen the evidence on tiered formularies as a managed care pharmacy

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**TABLE 1** Quality Ratings of Articles Overall and by Intervention

<table>
<thead>
<tr>
<th>Managed Care Pharmacy Interventions</th>
<th>Total Number of Articles</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>63</td>
<td>22</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Tiered formulary</td>
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<td>13</td>
<td>12</td>
<td>2</td>
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<tr>
<td>Prior authorization</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Step therapy</td>
<td>7</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Therapeutic interchange</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Drug utilization review</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Medication therapy management</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
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Effect of 6 Managed Care Pharmacy Tools: A Review of the Literature
Prior Authorization: Summary of the Literature

- PA is consistently associated with reductions in pharmacy utilization of and expenditures on the nonpreferred agent.
- The literature suggests that PA is an effective cost-management tool, but it is unclear whether patients are impacted positively or negatively (e.g., mixed findings on discontinuation rates).
- The PA literature consistently shows significant reductions in pharmacy utilization and spending and, when studied, does not increase other medical costs.
- Research on PA is needed to expand current evidence, including analyzing patient outcomes, patient satisfaction and quality of life, and administrative costs associated with PA policy.

PA is “an administrative tool normally used by a health plan or PBM that requires the prescriber to receive pre-approval for prescribing a drug in order for the drug to qualify for coverage under the terms of the pharmacy benefit plan.”

The purpose of PA is to change prescribing behavior and ultimately encourage appropriate use of medications and contain costs, and PA interventions were used by approximately 9 of 10 employer-sponsored pharmacy benefit plans in 2009.

Payers have used PA programs to direct coverage of high-cost, newer drugs to only those patients who demonstrate a medical need for the newer drug or are at risk of developing an adverse event that the newer drug is less likely to cause. For example, PA programs have been used for PPIs to limit coverage primarily to those individuals who are at high risk for an ulcer or gastrointestinal (GI) bleed or for those who demonstrate a medical need, such as sustained tissue damage in the case of cyclooxygenase 2 (COX-2) inhibitors. We reviewed 9 studies that examined the effect of PA programs on various outcomes. The results are summarized below.

Delate et al. (2005) examined the effect of a Medicaid PA program for proton-pump inhibitors (PPIs) on clinical and financial outcomes. Of nearly 8,000 members who attempted to fill a PPI, about 50% did not attempt to get PA, and of those, over 50% had a histamine-2-receptor antagonist (H2RA) claim instead. In terms of medical utilization, PPI users were more likely to have had at least 1 GI-related inpatient and ambulatory event in follow-up compared with nonusers, although there was no difference compared with H2RA users. The authors found that the number of PPI claims and expenditures decreased, while the number of H2RA claims and expenditures increased. Overall, this change was associated with a 50% decrease in antisecretory drug expenditures (PPIs and H2RAs) from $3.44 per member per month (PMPM) to $1.74 PMPM, producing annual antisecretory drug cost savings of $23.4 million for this Medicaid program of 1.2 million beneficiaries. These drug cost savings were realized without increases in either GI-related or total medical service costs for those beneficiaries who were denied coverage of a PPI by the PA intervention.

Four studies examined the effect of PA policies on antipsychotic or antidepressant medications. Three of the studies used 2 states in their analysis: Adams et al. (2009) and Zhang et al. (2009) used 1 state as a control for the other state initiating a PA policy; and Law et al. (2009) did not have a control state but instead examined the PA policy in 2 different states. Adams et al. found significant decreases in use of the nonpreferred selective serotonin-reuptake inhibitor (SSRI) post-PA, slight decreases in the number of Medicaid beneficiaries initiating therapy in the treatment state, and a nonsignificant change in the rate of discontinuity. Like Adams et al., Zhang et al. also reported nonsignificant differences in switching or augmenting the initial medication regimen between the 2 states; however, in contrast to Adams et al.’s findings, they found significantly higher adjusted hazards of discontinuing therapy post PA-policy. Law et al. found a significant drop in Medicaid’s market share for nonpreferred agents post-PA but found no significant changes in total Medicaid reimbursement of daily dose.

McCombs et al. (2002) examined the effect that revoking California’s Medicaid PA policy on SSRIs had on patient compliance and switching antidepressant therapies. The authors found that the likelihood of drug therapy completion significantly decreased from 23% with the PA policy to 21% after the PA policy was revoked. However, there was no change in the likelihood of patients switching therapies.

Fischer et al. (2004), Gleason et al. (2005), Hartung et al. (2004), and Stacy et al. (2003) examined the effect of PA
policies for COX-2 inhibitors. Gleason et al. (2005) found that a PA program for COX-2 inhibitors that limited coverage to patients with a documented risk for GI bleed was associated with pharmacy cost savings without an increase in GI-related medical costs. Among members of a large employer group’s health plan who were on a COX-2 inhibitor before the PA program and had no COX-2 inhibitor claims after the PA program was instituted, total pharmacy costs decreased significantly by $126 (40.0%) per member per quarter; these costs remained significantly lower throughout the year follow-up period. Conversely, for the subgroup who tried to fill a COX-2 inhibitor but were denied, per member pharmacy costs declined 48% and remained significantly lower in the year follow-up period. While medical costs initially declined 10.3%, overall medical costs increased in the second and third quarter. Taking into consideration PA program administration costs (including lost rebates), the authors calculated a net plan savings of $78,810 for 1 quarter.

Hartung et al. (2004) evaluated the intended and unintended effects of a Medicaid PA policy for celecoxib, a COX-2 inhibitor. From their interrupted time-series analysis, the authors found that the PA program significantly reduced utilization of celecoxib from 1.07 to 0.53 days; supply per person-year but was not associated with a change in utilization of other drug classes or ER visits. Fischer et al. (2004) utilized state-level data to compare COX-2 inhibitor use in state Medicaid programs with versus without PA programs. They found that states’ implementation of PA programs was associated with a significant decrease in the proportion of COX-2 inhibitor use by 11%, and significantly reduced the proportion of nonsteroidal anti-inflammatory drugs (NSAID) comprised of COX-2 inhibitors by 15%. This reduction in use corresponded to a significant decrease of $10.28 in spending per NSAID prescription after initiation of the PA program. Using a binary decision tree (i.e., maintaining PA with current criteria versus removing the PA) for their cost-effectiveness analysis, Stacy et al. (2003) showed that the health plan’s cost per success (i.e., no serious GI event) for COX-2 inhibitors with PA was $278 versus $422 without a PA policy.

While most of the reviewed studies examined the effect of PA policies on prescription drug expenditures and medical expenditures, the PA literature would be strengthened if studies that examined costs also included estimates of the administration and time costs associated with using a PA program. Studies that examine the effect of PA programs on prescription drug utilization should also include medical utilization (e.g., see Delate et al., Gleason et al., and Hartung et al.) to capture any possible spillover effects into health care utilization. Finally, other than Delate et al. (2005), none of the studies in our review examined the effect of PA programs on patient outcomes, such as satisfaction, and quality of life. Therefore, the PA literature could be strengthened if researchers examined these factors in future studies.

Step Therapy: Summary of the Literature

- Step-therapy interventions have been used to encourage the use of therapeutically equivalent, lower cost medications for several different therapeutic drug classes.
- Step-therapy interventions effectively encourage the utilization of first-step drugs.
- A few studies found that step-therapy interventions were associated with lower continuation rates or higher discontinuation rates.
- Most studies found that step-therapy interventions effectively lowered the prescription drug costs of the payers.
- Two studies examined the effect of step-therapy interventions on medical utilization and cost with mixed results.
- There is a paucity of research examining the effect of step therapy on medical utilization and costs and clinical and humanistic outcomes.

Step therapy is “designed to encourage the use of therapeutically equivalent, lower-cost medications (i.e., first-line therapy) before “stepping up” to more expensive therapy (i.e., second-line therapy).” We reviewed 7 studies that examined the effect of step-therapy programs on a variety of outcomes for different drug classes, including PPIs, NSAIDs, antidepressants, and antihypertensives. All of the step-therapy studies were rated “fair” in terms of quality except 1, which was rated “good.”

All of the studies found that programs with a step-therapy policy had a higher number of members utilizing (or switching to, in the case of a new policy) the first-step drugs (e.g., generics) than plans that did not use step therapy. Additionally, a few studies found that the days of drug therapy or continuation rates were lower in plans with step-therapy groups than those without, while Mark et al. (2009) found an initial decrease in days supply of the more expensive second-line therapy, but then found the number of days of antihypertensive drug therapy increased over time and eventually exceeded the comparison plans (nonstep therapy) after 5 quarters. Similarly, 2 studies found that discontinuation rates were higher for step-therapy groups (Mark et al., Panzer et al.[2005]) than comparison groups without step therapy. Yokoyama et al. (2007) reported that within 12 months of follow-up, 51% of those who received other antihypertensives as an index therapy switched to or added the originally averted antihypertensive, angiotensin receptor blocker (ARB).

As health plans intended, step-therapy programs were shown to decrease prescription drug costs for the payer. Dunn et al. (2004) found a 9.0% difference in the drug cost per day of therapy between the intervention and the comparison group that results in a $0.36 PMPM savings for the plan.
While Dunn et al. did report that step therapy was shown to result in plan savings, the authors did not include administrative costs of the program or medical costs. Similarly, Panzer et al. found a net reduction of $0.26 PMPM for a generic step-therapy program for SSRIs. Yokoyama et al. found a mean antihypertensive drug cost per day was 35.9% lower in the intervention group than in the comparison group, and the ARB step therapy was associated with a $43.91 drug cost savings per patient over 12 months. Conversely, Mark et al. found an initial decrease in drug spending after a step-therapy intervention, but then spending grew over time at a rate similar to the nonstep-therapy plans. While Mark et al. and Yokoyama et al. examined antihypertensives, the step therapy was for either ACE inhibitor or ARB in Mark et al.’s study, whereas Yokoyama et al. studied only an ARB program, which may account for the differences.

Two studies with important limitations examined the effect of step-therapy programs on medical utilization and costs. Mark et al. found that a step-therapy program for antihypertensive drugs was associated with an increase in outpatient visits and positively associated with ER visits compared with plans without a step-therapy program, though they did not examine cardiac-specific utilization. Panzer et al. developed an economic model to determine the effect of a generic step-therapy formulary versus an open formulary. They found a significant increase in medical costs associated with implementing a generic step-therapy requirement for SSRIs compared with not having a step-therapy program; overall, this translated to an increase in total plan spending.

Cox et al. (2004) and Motheral et al. (2004) surveyed members to determine the effect of step therapy on the medication members received, and who contacted the physician. They found that approximately 40% of members reported that the pharmacist contacted their doctors, while the remaining 60% contacted their doctors themselves. Additionally, Cox et al. and Motheral et al. found that 11% and 17% of members, respectively, reported receiving no medication, and 11% and 16% of members reported paying OOP for the prescription. Motheral et al. also found that satisfaction was higher among brand versus generic drug users but significantly lower for those paying OOP for the brand and receiving no medication compared with those who received a generic drug.

While a few of the reviewed studies examined the effect of step therapy on medical utilization and costs and with mixed results, further research examining the overall impact of step-therapy programs is needed. Additionally, research on step-therapy programs should examine whether the interventions result in any spillover effects and the effect of such programs on patient outcomes. The literature would also be strengthened if the cost estimates included costs of administering the program.

### Therapeutic Interchange: Summary of the Literature

- The literature on therapeutic interchange examines programs for several different therapeutic drug classes as well as voluntary and mandatory programs.
- Therapeutic interchange programs effectively shift patients to preferred drugs, although some studies observe patients switching back to the nonpreferred drug.
- The findings on the effects of therapeutic interchange programs on costs and clinical outcomes are mixed.
- While there is a paucity of research on the effect of therapeutic interchange on clinical and humanistic outcomes, the use of therapeutic interchange as a tool has declined with the adoption of tiered benefit designs and step therapy and therefore is a low priority.

Therapeutic interchange programs, also referred to as “switch” or “conversion” programs, encourage the use of either formulary or preferred drugs by switching from one agent to another agent on the formulary that is less expensive for the managed care organization, but equally effective for the patient; the interchange can be from brand to brand, brand to generic, and prescription to over the counter (OTC). The authors reviewed 5 studies examining the effect of therapeutic interchange programs in managed care all of which were rated fair in terms of study quality. Studies examined therapeutic interchange programs for a variety of therapeutic classes, including estrogen replacement therapy, antihistamines, statins, PPIs, and warfarin. We also reviewed studies that examined therapeutic interchange programs that mandate systemwide conversions rather than specific to a drug class. Studies have also compared plans with mandatory conversions versus voluntary conversion, as well as therapeutic interchange programs that aim to channel patients to the preferred drug, while granting exceptions when appropriate and requested by the prescriber.

Andrade et al. (2000) evaluated the impact of a formulary switch from conjugated estrogens to esterified estrogens using a 3-stage intervention (e.g., notification letter, provided list of affected patients, physicians required to complete form to justify need for conjugated estrogen). As desired by the health plan, the program shifted prescribing rates substantially from 3,139 conjugated and 413 esterified estrogen prescriptions to 53 and 3,719 conjugated and esterified estrogen prescriptions, respectively. The authors found that 72% of patients switched to esterified estrogens, 20% discontinued therapy, and 5% remained on conjugated estrogen therapy. Among those who switched, the probability of switching back to conjugated estrogens was 12% after 6 months and 15% after 2 years. Additionally, the overall probability of discontinuing the esterified estrogens was 16% after 6 months and 32% after 2 years. The number of physician visits was significantly
Effect of 6 Managed Care Pharmacy Tools: A Review of the Literature

greater for users who switched compared with those who did not, although there was no difference in hormone replacement therapy-related visits. The health plan’s prescription drugs savings for the conversion was estimated at $2.43 per patient.

Nelson et al. (2000) studied the clinical and humanistic outcomes of a conversion program for gastroesophageal reflux disease (GERD) patients from omeprazole to lansoprazole in an MCO.50 The authors reported that for the 105 patients who completed both survey interviews, post-conversion symptom severity was significantly higher and overall satisfaction significantly lower than at pre-conversion levels.

Fugit and Resch (2000) and Witt et al. (2003) examined conversion program interventions in which patients were converted at the time of a pharmacist-managed outpatient clinic visit and assessed for conversion outcomes at follow-up visits.51,52 Fugit and Resch assessed the effects of a therapeutic interchange conversion in a Veteran’s Administration (VA) medical center for statins (HMG-CoA), specifically for low-dose simvastatin to lovastatin. Among the 96 patients eligible for evaluating the conversion, the authors found no statistically significant differences between the 2 different conversion (simvastatin 5 milligrams (mg) to lovastatin 5 mg, and simvastatin 10 mg to lovastatin 10 mg) groups’ lipid and liver function tests. Of 157 patients eligible for evaluating their attainment of low-density lipoprotein cholesterol (LDL-C) goals, 52% were not at LDL-C goals at initial assessment, but this decreased to 38% and 26% by the 3-month and 6-month follow-up visit, respectively.

Witt et al. did a study of a conversion for brand to generic warfarin for 2,299 patients of a clinical pharmacy anticoagulation service in a group-model health maintenance organization (HMO). The overall differences in the calculated time that international normalized ratio (INR) values were below (22.6% before vs. 26.1% after switch, P<0.001) and within (65.9% before vs. 63.3% after switch, P<0.001) the therapeutic INR range was statistically, but not clinically, significant. The authors also report that a significant proportion of patients (72%) experienced a 10% or greater change in therapeutic INR control after the conversion (i.e., INR control improved for 33% of patients but worsened for 39% of patients). The authors determined that the difference in total treatment costs associated with brand name versus generic warfarin was $3,128 per 100 patient-years. Additionally, they concluded that the economic impact of warfarin conversion was highly dependent on costs associated with treating non-fatal adverse events.

Benedetto et al. (2000) assessed the impact of different interventions designed to shift prescribing from fexofenadine to loratadine for HMO members.53 The 3 interventions consisted of a mandatory lockout (HMO A), a voluntary switch consisting of information letters to physicians, list of affected patients, and $10 manufacturer coupons (HMO C), and a voluntary switch identical to HMO C with an additional letter sent to patients (HMO B). HMO D had no restrictions on member benefits for antihistamines and served as the control. The 3-intervention HMOs all had similar market shares of antihistamines before the interventions, though the magnitude of shifts in prescribing patterns after the intervention varied greatly across the 3 intervention HMOs. HMO A experienced the largest increase in market share (prescription utilization) of fexofenadine (19% to 65%) and the largest decrease in market share of loratadine (62% and 9%). HMOs B and C, the voluntary switch programs, both experienced a modest increase of fexofenadine utilization (B: 15% to 21%; C: 21% to 24%) and a decline in loratadine utilization (B: 68% to 59%; C: 71% to 65%). Lastly, the average cost per antihistamine prescription decreased 22.3% at HMO A, while at HMOs B, C, and D, average antihistamine prescription costs continued to rise.

Therapeutic interchange programs have successfully shifted patients, at least initially, to the desired therapeutic alternatives under both mandated50–53 or voluntary programs50–55 although the voluntary programs observed that over 10% of patients switched back to their original drug. The findings on the cost savings associated with therapeutic interchange programs were mixed, as were the studies that examined clinical outcomes (although the studies examined different therapeutic classes). The effect of therapeutic interchange programs was difficult to assess in the aggregate, since the studies examined conversion programs for different therapeutic classes, although Benedetto et al. examined several different health plans’ conversion programs for antihistamines.

Only a few studies examined humanistic outcomes, and there were mixed findings on the clinical outcomes of conversion programs, which could indicate the need for further research on therapeutic interchange. However, the utilization of therapeutic interchange as a managed care pharmacy tool has declined with the widespread adoption of tiered benefit designs and step therapy, making the need for additional research in this area a low priority.

Drug Utilization Review: Summary of the Literature

- DUR interventions targeted at contraindicated or inappropriate medications appear to result in increased discontinuation rates for the target drug(s).
- While managed care pharmacists report widespread use of DUR as a tool, there is limited published research examining the effect of DUR as an intervention in the past 10 years.
- Few studies examine the effect of DUR, and those that have are of limited quality.

DUR is synonymous with drug use evaluation (DUE), which is defined as an authorized, structured, ongoing review of
physician prescribing, pharmacist dispensing, and patient use of medication. DUR involves a comprehensive review of patients’ prescription and medication data before, during, and after dispensing to ensure appropriate medication decision making and positive patient outcomes, and the intervention can occur at the point of sale or point of dispensing, including e-prescribing.

The authors reviewed 4 published articles that examined retrospective DUR programs in the period covered by this review, and 3 of the 4 articles examined the intervention in publicly insured populations. The DUR articles were of lower rigor compared with the literature in other areas with 2 articles rated as “fair” and 2 rated as “poor” based on our rating scale. The findings from the 2 studies rated as “fair” quality are described first, followed by the 2 studies rated as “poor.”

Gleason et al. (2004) assessed the impact of a DUR alert letter program on metformin discontinuation rates in 566 patients with a metformin claim and an absolute contraindication to metformin therapy who were members of a large health plan and the affiliated PBM as compared with over 15,000 members on metformin in the comparison group. They found the metformin discontinuation rates at 9-months follow-up for the intervention group and comparison groups to be 37.3% and 20.0%, respectively (P < 0.001). They also found the rate of discontinuation was 84% higher in the intervention group (P < 0.001). Gleason et al. estimated, taking into account the program administrative costs, that the potential cost avoidance of the metformin alert letter for the control group was $6,122 per year for 566 intervention patients.

Using aggregated state Medicaid data, Moore et al. (2000) found no significant differences in prescriptions per recipient, the number of drug recipients, or average prescription cost between states with or without a retrospective DUR between 1985 and 1992. However, drug expenditures per recipient and total drug expenditures were 4.9% and 6.5% lower, respectively, in states with DUR programs compared with states without DUR programs. The authors also report no significant spillover effects on nonpharmaceutical expenditures. The authors also examined if the length of time a DUR has been in operation affected drug expenditures or utilization and found that older DUR programs were associated with a decrease in the number of drug recipients (4.4%) and total drug expenditures (5.4%).

Seltzer et al. (2000) used a pre/post-study design to examine the effect that an intervention letter to physicians had on polypharmacy. Among the 0.27% of patients (n = 244) who had excessive dosage, prolonged treatment (defined as over 4 months), and/or concurrent therapy with 2 or more sedative/hypnotics agents, the authors found that 40% of the prescribing physicians (n = 84) agreed that the sedative-hypnotic use was excessive. Approximately 1 year after the intervention letter, the authors found that the physicians had discontinued sedative-hypnotic use for 47% of patients, translating to a favorable response by approximately 20% of physicians who responded to the intervention letter. The authors did not examine cost and also examined sedative-hypnotic use for only a 7-month period in 1998 and therefore may have missed seasonal differences of sedative-hypnotic use.

More recently, Starner et al. (2009) focused exclusively on beneficiaries in a Medicare Part D benefit plan in 4 states to identify potentially inappropriate medications in an elderly population in 2007. The authors used the National Committee for Quality Assurance (NCQA) list of drugs to be avoided in the elderly (DAE), which is also part of the HEDIS measure, and focused their findings on the top 6 drug classes that accounted for nearly 90% of the DAE claims: estrogens, propoxyphene, nitrofurantoin, muscle relaxants, antihistamines, and anticholinergics. An intervention letter was sent to the prescribing physicians of the 5.2% of the patient population who had a 7-day (or longer) script for a DAE during a 7-month period. After 6 months, the authors found that 49% of patients no longer had a DAE script; the discontinuation rate ranged from 31% (estrogens) to 67% (anticholinergics) across the 6 drug classes.

Neither Starner et al. nor Seltzer et al. had control groups, making it difficult to assess the impact of a DUR on pharmaceutical use. Furthermore, as Starner et al. note, the fact that many of the drugs they evaluated could be used for short-term therapy made it difficult to attribute their discontinuation to the DUR (versus the patient completing the course of therapy). Finally, by relying on claims for the analyses, we do not know if the observed discontinuation truly reflects the patients’ medication-taking behaviors.

The few studies of DUR interventions provided findings of limited rigor. DUR interventions targeted at contraindicated or inappropriate medications appear to result in increased discontinuation rates for the target drug(s). While managed care pharmacists report widespread use of DUR as a tool, there is limited published research examining the effect of DUR as an intervention in the past 10 years. Few studies have examined the effect of DUR, and those that have are of limited quality.

Medication Therapy Management: Summary of the Literature

- MTM programs and interventions are associated with improvements in several clinical measures including lower blood pressure, lower LDL-C levels, and HEDIS hypertension measures.
- A few studies examine the effect of MTM on health care utilization (e.g., hospitalization, ER visit) with mixed results.
- The effect of MTM on the number of medications (i.e., polypharmacy) and the medication costs are mixed.
Additional rigorous studies of the effect of MTM on clinical and humanistic outcomes would strengthen the evidence base for MTM.

Future research on the savings associated with or costs avoided by MTM should incorporate the program and administration costs (e.g., pharmacist salaries).

There have been several studies of MTM in managed care settings, but there is relatively little published literature on the effect of Medicare Part D MTM despite the requirement that all Medicare Part D plans offer MTM to eligible beneficiaries since 2006. The evidence on MTM is difficult to summarize because it often entails a variety of diverse and complex interventions that are not readily comparable to one another even though they all fall under the umbrella of MTM. Furthermore, many of the MTM studies have poor comparison or control groups, posing a weakness in terms of making a direct link to the outcomes measured. While there have been several studies of MTM in managed care settings, there is relatively little published literature on the effect of Medicare Part D MTM programs, given that all Medicare Part D plans have been required to provide MTM to eligible beneficiaries since 2006. Accordingly, there are several areas in which adequate literature does not exist for MTM in managed care settings, including examining the extensive evaluative data on the Medicare Part D plans’ MTM programs, furthering the strength of the evidence on key clinical outcome measures, and improving the rigor of the study methodologies to strengthen the evidence base. Additionally, there is limited research on patient satisfaction and quality of life measures associated with MTM in managed care.

The Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA) required prescription drug plans to offer MTM programs to eligible, high-risk Medicare beneficiaries beginning in 2006. MTM is a distinct service or group of services that optimize therapeutic outcomes for individual patients. There are several challenges to synthesizing the evidence on MTM programs in managed care (and other) settings, including the variations on the services and interventions provided, different intervals and frequencies, and which outcomes are desired. For example, some studies examined MTM programs that targeted patients with specific conditions or risks, whereas other studies examined MTM programs targeted at patients with multiple comorbidities. The studies examined the effect of MTM on a variety of outcomes, including clinical, drug therapy problems, drug utilization, HEDIS measures, medical utilization, drug costs, and total costs. One study conducted a cost-effectiveness analysis of MTM programs. Most of the studies examined MTM programs utilizing community pharmacists to provide MTM, either in ambulatory clinics or retail pharmacies, although a few studies examined MTM programs involving primarily telephone or mailed interventions. We reviewed 11 studies of either MTM programs in managed care settings or MTM provided to MCO members. The distribution of the MTM study quality rates were good (n = 4), fair (n = 6), and poor (n = 1). The results of the studies are described below in order of the quality of the studies.

Borenstein et al. (2003) compared the effectiveness of a physician-pharmacist co-management of uncontrolled hypertension for 197 patients. The intervention group was comanaged by their primary care provider (PCP) and a clinical pharmacist who together provided patient education, made treatment recommendations, and provided follow-up. The intervention group and usual care (i.e., control) groups experienced significant reductions in blood pressure post-intervention, and the reduction in systolic blood pressure was greater in the intervention group after adjusting for differences at baseline. More patients in the intervention group achieved blood pressure control than the usual care group, and average provider visit costs per patient were higher for the usual care group compared with the intervention group.

Okamoto and Nakahiro (2001) measured the clinical, economic, and humanistic outcomes associated with a pharmacist-managed hypertension clinic compared with a physician-managed clinic in a managed care organization (MCO). The study sample consisted of 330 patients: 164 in the treatment group and 166 in the control group. They found statistically significant decreases in systolic and diastolic blood pressure within the treatment group between baseline and final visit, as compared with the control group for which there was no significant change between baseline and follow-up. The between group comparisons showed mean systolic blood pressure decreases statistically lower for treatment versus control group after 6 months. In terms of quality of life, there was a statistically significant higher score for the role-physical domain of the short form (SF)-36 (e.g., for control vs. treatment group after 6 months). The average number of clinic visits was significantly higher in the treatment group versus control group (5.25 vs. 1.41), and there were 4 ER visits in the control group versus none in the treatment group. There was no significant difference in the average number of antihypertensive drugs per patient between the treatment and control groups at baseline or follow-up. In terms of cost, there was no statistically significant difference in mean drug cost per patient, cost of hospitalization, or total costs per patient between groups. Lastly, clinic visit costs were significantly higher in treatment group versus control group, and the average cost per patient for ER visits was significantly lower in the treatment versus control group.

Planas et al. (2009) evaluated the effect of a randomized, controlled trial of a 9-month community-pharmacy-based MTM program on 52 MCO patients with diabetes and hypertension receiving care from pharmacists in 5 regional chain
pharmacies. The authors found that the intervention group's mean systolic blood pressure (SBP) decreased 17.32 millimeters mercury (mmHg), whereas the control group's mean SBP increased 2.73 mmHg (P = 0.003). Furthermore, the intervention patients were 12.92 times more likely to achieve goal BP (P = 0.021) than the control group. There was no statistically significant difference in adherence rates between intervention and control group.

Welch et al. (2009) assessed the impact of a group model HMO's Medicare Part D MTM program that used telephone management to provide MTM to home-based patients for 539 Medicare Part D beneficiaries with 2 or more conditions (1 of which was high risk), 5 or more Part D drugs, and over $4,000 in expected annual drug costs. Although there was no difference in ER visits, the authors found that beneficiaries who opted-in were less likely to die (adjusted odds ratio [OR] = 0.5), more likely to have had a hospitalization (adjusted OR = 1.4), and have higher medication costs (adjusted OR = 1.4) during follow-up compared with beneficiaries who opted out.

Etemad and Hay (2003) conducted a cost-effectiveness analysis, prior to Medicare Part D, to estimate the effect that community pharmacists could have on medication-related morbidity and mortality in the elderly if comprehensive pharmaceutical care were to be included in a Medicare drug benefit program. They estimated that a pharmaceutical care benefit could increase the number of patients who achieved the HEDIS 2001 hypertension goal by 59% and the HEDIS 2001 hyperlipidemia goal by 52%. The total health expenditures for intervention patients decreased from $11,965 to $8,197 per person (n = 186, P < 0.001) and exceeded the cost of providing MTM by more than 12 to 1.

Stebbins et al. (2005) measured generic drug use, savings, and patient medication access for 520 Medicare-eligible, low-income elderly patients with high drug costs and multiple diseases and medications who participated in a pharmacist-directed, multidisciplinary clinic. The clinic assesses patients' medications, aims to decrease OOP costs, and ensures patients receive cost-effective, appropriate medications. In 1 year, pharmacists provided 1,297 interventions (2.5/patient), all of which were accepted by physicians. The most common interventions provided were pharmaceutical industry-sponsored patient assistance programs, generic substitution, and therapeutic interchange. The authors also found that the average ratio of generic drug use to total prescriptions for patients increased from 51% to 56%. After implementation, the average OOP expense was reduced to $60/patient month, a 68% decrease, representing an average of $1,500 OOP savings per member per year. Lastly, they found that 215 patients (41%) reported that they had discontinued or would soon discontinue use of a prescribed drug because of cost; among these, 186 (87%) were able to continue indicated drugs after clinic interventions.

Stockl et al. (2008) measured the effect of an MTM intervention comprised of a patient-specific mailing to prescribers aimed at increasing statin use for 1,340 members of Medicare Part D plans (Medicare Advantage plans and stand-alone prescription drug plans) administered by a PBM in several states. The authors found that significantly more of the MTM group started a statin medication compared with the comparison group (12.1% vs. 7.3%, respectively; P = 0.001), and the odds of initiating a statin were 65% higher in the MTM group than the comparison group (P = 0.006). The authors estimated that the average number of 30-day equivalents dispensed, Medicare Part D costs, Medicare Part D copayments, and all copayments were significantly different for the MTM versus control groups, although the intervention group did not always have decreased costs.
number of members requiring interventions to prevent 1 major cardiovascular event was 220, and estimated coronary event cost avoidance is $12,323 per 220 members who received the intervention, after subtracting the program administration and drug therapy costs.

Barnett et al. (2009) with a far less rigorous design simply examined the trends over a 7-year period in MTM interventions, including pharmacy reimbursement and estimated cost avoidance (ECA). The authors found over a 60% increase in mean (SD) payment from $7.65 ($3.03) in 2000 to $12.28 ($6.65) in 2006. They also found that ECA average (SD) per claim increased from $24.18 ($139) to $429 ($2,421) from 2000 to 2006; the significant change is attributed to a few high-cost, high-impact claims. This study was a descriptive study with several limitations, including limited information on the effect of MTM other than ECA, which is a weak measure of pharmacist-reported costs avoided.

The evidence on MTM is difficult to summarize because it often entails a variety of diverse and complex interventions that are not readily comparable to one another even though they all fall under the umbrella of MTM. Furthermore, many of the MTM studies have poor comparison or control groups, posing a weakness in terms of making a direct link to the outcomes measured. All the same MTM programs and interventions have been associated with improvements on several clinical measures (e.g., BP, LDL-C, HEDIS hypertension measures). A few studies have examined the effect of MTM on health care utilization (e.g., hospitalization, ER visit), the number of medications, and medication costs with mixed results. While there have been several studies of MTM in managed care settings, there is relatively little published literature on the effect of Medicare Part D MTM programs, given that all Medicare Part D plans have been required to provide MTM to eligible beneficiaries since 2006. Accordingly, there are several areas in which adequate literature does not exist for MTM in managed care settings, including examining the extensive evaluative data on the Medicare Part D plans’ MTM programs, furthering the strength of the evidence on key clinical outcome measures, and improving the rigor of the study methodologies to strengthen the evidence base. Additionally, there is limited research on patient satisfaction and quality of life measures associated with MTM in managed care.

Discussion

Our review of the extant literature from the past 10 years for 6 key managed care pharmacy interventions or tools provides an in-depth understanding of the state of the evidence, which can serve to inform decision makers about the impact of these strategies on several outcomes. PBMs and Medicare stand-alone prescription drug plans are charged with effectively and efficiently managing the pharmacy benefit of a payer’s members. Therefore, they are motivated to focus on outcomes directly associated with the prescription drug benefit and do not focus on cost shifts to the payer and patient or on medical utilization.

Future Research

Given that PBMs and MCOs are charged with effectively and efficiently managing the pharmacy benefit for public and private payers, it is understandable that cost concerns are a major focus of research on managed care pharmacy interventions or tools. The findings from the extant literature for several of these interventions, while valid and extensive, primarily examine the effect of these interventions on utilization and cost outcomes. Consequently, there is an opportunity and need for additional literature on certain outcomes that are minimally addressed in the literature but are likely important outcomes of interest to decision makers considering these tools or interventions.

While the literature extensively examines the cost or savings associated with the interventions, little research includes either medical costs or other health care costs to appropriately assess whether the intervention results in a “spillover effect.” Similarly, the cost savings reported commonly do not include the program administration costs, and even more rarely do the studies include the pharmaceutical manufacturer rebates in the cost estimates, although the direction of that bias is unclear. These gaps in information on the cost estimates limit the ability of decision makers to understand the true costs of these interventions.

While private and public payers expect improved outcomes from managed care interventions, especially cost outcomes, there is still a paucity of research on clinical and humanistic outcomes, except for MTM. Further research examining the effect of managed care pharmacy interventions on clinical and humanistic outcomes would strengthen the evidence base on these interventions and aid decision makers.

Since MTM is significantly different from other interventions, the gaps are unique. While there has been research on the clinical and humanistic outcomes of MTM, the rigor of the studies has often been limited due to the small sample sizes and the challenges obtaining appropriate comparison groups. Additionally, since MTM is a complex intervention that can be operationalized in several ways, the literature could benefit from consistent and complete descriptions of the interventions. There is a great opportunity posed by the Medicare Part D requirement that plans offer MTM to eligible, high-risk beneficiaries; some research has been published on the effect of their programs; however, given the number of Medicare Part D plans, there should be more studies published on these programs in the future.

While the review of the literature focused on the effect of managed care pharmacy tools on various patient and payer
outcomes, there are studies that explore the burden of these interventions (i.e., PA, therapeutic interchange) on physicians’ and pharmacists’ time and associated cost, for example.\textsuperscript{71,72} More rigorous studies of the effect of managed care pharmacy interventions on clinicians’ time and the associated cost may provide decision makers with a valuable angle on the effect of such interventions throughout the system of care.

The aforementioned gaps are areas of needed research to provide decision makers with a thorough examination of these tools. There are legitimate challenges to conducting the needed research and provide the reasons why that research has been limited. For example, PBMs typically only have access to the pharmacy claims data and not the medical claims data. Additionally, neither pharmacy claims nor medical claims data include clinical outcomes measures, further limiting the ability of an MCO-based researcher to examine the clinical outcomes of specific interventions with the exception of certain managed care models in which the providers are integrated with the payer and therefore have access to electronic medical records.

Limitations
There are several limitations to this review. Despite a broad and multimethod approach for identifying literature meeting the selection criteria for this review, we may have missed relevant articles. Additionally, we bound certain interventions more stringently than others given the objectives of the review, which were to examine the effect of managed care pharmacy interventions. As a result, we narrowly defined several of the managed care interventions, while recognizing that individuals define the scope of managed care pharmacy differently. Therefore, for example, for MTM we excluded studies that examined pharmacist-provided MTM in the community pharmacy that was not provided to managed care patients or provided in a managed care setting (e.g., integrated group model HMO). Although we reviewed the literature on 6 managed care pharmacy interventions, there was wide variance in the number of studies for each intervention, especially tiered formularies (n = 27) compared with DUR (n = 4). Lastly, a limitation of this review is the challenge of synthesizing the evidence for very diverse managed care pharmacy interventions with different features, objectives, populations, and methods.

Conclusion
There is strong evidence for the effectiveness of several managed care pharmacy tools for achieving intended outcomes such as increased utilization of preferred drugs, formulary compliance, and decreased prescription drug spending. Although these tools achieve reductions in utilization and expenditures, it is unclear whether patients are impacted positively or negatively. While some studies examine the effect of managed care pharmacy tools on medical utilization and costs, the results are mixed. Unlike other interventions, MTM interventions demonstrate improvements on several clinical measures, although the evidence needs to be expanded, especially with regard to Medicare Part D MTM programs. While there is a breadth of literature on some managed care pharmacy interventions, there are several interventions that require additional research, especially with regard to clinical and humanistic outcomes, in order to provide decision makers with a more comprehensive understanding of the value of managed care pharmacy tools.

REFERENCES


The aim of the literature review was to examine the effect of select managed care pharmacy interventions on various outcomes based on the peer-reviewed literature from the past 10 years. The 6 interventions were drug utilization review, medication therapy management, prior authorization, step therapy, therapeutic interchange, and tiered formularies. This section briefly describes the approach Abt Associates, Inc., used to identify and select articles for review. Exhibit 1 provides a flow diagram of the study identification and the inclusion and exclusion process.

Search Strategy
To identify potentially relevant articles, Abt Associates search strategy consisted of 2 approaches: perform a PubMed search and scan the reference lists of key literature reviews of managed care pharmacy interventions. Each approach is detailed below.

PubMed Search
Abt Associates performed a search in PubMed to identify potentially relevant, peer-reviewed literature published between January 1, 2000, and December 31, 2009, using a combination of search terms to identify relevant literature. We began by characterizing the setting through the use of the PubMed medical subject heading (MeSH) term “managed care programs” or “health maintenance organization” or “preferred provider organizations” to identify the literature in managed care. We then identified articles using relevant methodologies for this literature review by using the search string “outcome or effect or intervention study or comparison or evaluation” to characterize the relevant study designs.

These 2 searches were combined and used as qualifiers for each of the 6 interventions. Although “drug utilization review” is a MeSH term, we also searched similar and expanded terms to identify potentially relevant articles on each of the interventions. A total of 143 unique articles were identified (Exhibit 2). Unfortunately, PubMed was a poorly sensitive index for identifying relevant articles on managed care pharmacy interventions, which is the reason we used the subsequent strategies to identify relevant literature.

Scan Relevant Review Articles’ Bibliographies
To further expand our search, Abt Associates reviewed the bibliographies of relevant review articles identified through our literature review to uncover any articles that were not identified through the aforementioned searches. The bibliographies of 6 review articles were scanned for relevant articles on the select interventions and met the selection criteria.

Across the 6 review articles, there were approximately 250 unique articles on various managed care pharmacy interventions, 166 of which were published between 2000 and 2009. Furthermore, a subsample of these articles examined the selected 6 interventions of interest for this review.

Targeted Search of Relevant Journals
Abt Associates also conducted a focused search of the Journal of Managed Care Pharmacy (JMCP) and Managed Care magazine’s peer-reviewed section. This search was conducted to detect articles not identified through the PubMed search. Using the approaches detailed below, each journal was scanned using criteria similar to those employed in the PubMed search, narrowing the articles by setting, study type, and only including those that were relevant to the select interventions. JMCP was reviewed through a scan of the “JMCP Article Index by Subject Category” prepared by the journal and available on its website. This index categorizes the entire archive of JMCP articles, editorials, commentaries, letters, and supplements from the July/August 1995 issue through the December 2009 issue. The index was scanned for relevant articles from the past 10 years. Lastly, the American Journal of Managed Care was scanned for potentially relevant articles, although the sensitivity of the journal’s search engine was limited.

Recommended Articles from Experts
Given the potential limitations of the search strategy described above, we also encouraged members of the AMCP advisory board for this project to recommend other articles for review. In particular, Abt Associates asked for recommendations that appeared to meet our selection criteria but may not have been initially identified by the other search strategies. Peer reviewers also suggested articles that were not identified from the initial literature search.

Selection Criteria
The following selection criteria were used for selecting across all interventions; additional, tailored selection criteria were delineated for each intervention.

Inclusion Criteria:
- Published between January 1, 2000, and December 31, 2009
- English-language article
- Research study examining “effect” or “impact” of the intervention, regardless of the outcome of interest
- Managed care setting, population, or data

Exclusion Criteria:
- Non-U.S.-based study or intervention
- Not evaluations or studies of the effect of the interventions (e.g., editorial, review)
- Inpatient hospital setting
Refined Selection Criteria for Specific Interventions. The following is a more detailed description of the refined selection criteria that were employed for 4 of the interventions to ensure the relevance of the literature for this study:

- **Therapeutic Interchange.** The primary aim was to understand the value of therapeutic interchange or substitution as a managed care pharmacy intervention; that is, where the payer is driving the substitution. Therefore, we excluded studies where the provider (e.g., hospital, clinic, etc.) drove the therapeutic interchange.

- **Tiered Formularies.** Given the focus on the effect of tiered formularies, we excluded studies that focused simply on cost sharing (e.g., copay changes), unless the changes to the cost-sharing structure were in association with a change to, addition of, or removal of a tiered formulary.

- **Medication Therapy Management (MTM).** There is considerable discussion on what MTM consists of (or not), including whether or not MTM should be provided face-to-face. AMCP’s Validation Study on MTM73 suggested that MTM not be exclusively provided face-to-face. Since the objective of this study is to review the evidence on the effect of managed care pharmacy interventions on various outcomes, we have refined the focus for MTM studies to include studies of MTM in managed care settings or for managed care patients, excluding studies of pharmacists providing MTM in community pharmacies or medical centers (e.g., Veteran’s Administration). We acknowledge that defining MTM this way is narrow; however, the authors believe it is justified given the objective of focusing on the effect of managed care pharmacy interventions.

- **Drug Utilization Review (DUR).** While there appears to have been a substantial body of literature on the effects of DUR prior to 2000, we identified few articles examining the effect of DUR as a managed care intervention from 2000 through 2010. However, we did identify studies that examined, for example, the effect of an intervention for prescribers that was developed based on the

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**EXHIBIT 1** Flow Diagram of Study Identification, Inclusion, and Exclusion

- **PubMed search**
  - 143 articles published 1/1/00-12/31/09

- **Targeted managed care journals**
  - 68 articles published 2000-2009

- **6 review articles’ bibliographies**
  - 166 articles published 2000-2009

- **Experts identified**
  - 10 articles published 2000-2009

- **Experts identified**
  - 13 more articles published 2000-2009

- **PubMed-identified articles**
  - 126

  - 100 not on interventions of interest
  - 11 not evaluation or impact studies
  - 12 not evaluating intervention
  - 6 not in managed care setting
  - 4 not in managed care setting
  - 2 community pharmacy-provided medication therapy management without managed care payer
  - 9 provider-driven (e.g., hospital, clinic, pharmacist) for therapeutic interchange
  - 1 not in the United States

- **Reviewed and rated**
  - 62 unique studies

  - Drug utilization review (n = 4)
  - Step therapy (n = 7)
  - Prior authorization (n = 9)
  - Therapeutic interchange (n = 5)
  - Tiered formularies (n = 27)
  - Medication therapy management (n = 11)

- **Excluded 148 articles**
  - 116 not on interventions of interest
  - 4 not in managed care setting
  - 28 not evaluations or impact studies

- **Excluded 29 articles**
  - 12 not evaluating intervention
  - 6 not in managed care setting
  - 2 community pharmacy-provided medication therapy management without managed care payer
  - 9 provider-driven (e.g., hospital, clinic, pharmacist) for therapeutic interchange
  - 1 not in the United States

- **Full-text articles assessed for inclusion**
  - n = 79 articles

- **Excluded 126 PubMed-identified articles**
  - 100 not on interventions of interest
  - 11 not evaluation or impact studies
  - 4 not on interventions of interest
  - 28 not evaluations or impact studies

- **Excluded 148 articles**
  - 116 not on interventions of interest
  - 4 not in managed care setting
  - 28 not evaluations or impact studies

- **Excluded 29 articles**
  - 12 not evaluating intervention
  - 6 not in managed care setting
  - 2 community pharmacy-provided medication therapy management without managed care payer
  - 9 provider-driven (e.g., hospital, clinic, pharmacist) for therapeutic interchange
  - 1 not in the United States
the 3 reviewing authors. The group of readers compared the completed templates for consistency and resolved any discrepancies, which were primarily on the level of detail provided, before reviewing the remaining articles.

**Rating the Literature**

The readers developed quality rating criteria to better distinguish between stronger and weaker studies within the managed care pharmacy literature. The criteria were developed iteratively by 3 of the authors (Shoemaker, Pozniak, Subramanian) based on an initial review of the types of research designs in this literature. Once consensus was reached, 2 of the reviewing authors (Pozniak, Subramanian) reviewed all of the summaries and assigned 1 of 3 quality ratings to each: good, fair, poor. The 2 reviewers resolved discrepancies in ratings (inter-rater reliability was 85%) after discussion, and minor adjustments were made to the criteria to provide further clarification. Exhibit 3 shows the 3 quality levels, the methodological rigor associated with each, and mitigating factors that may also affect a study’s rating.

The results of quality rating of the studies are shown in Table 1 of the review. Nearly one-third of the articles were rated “good,” over half (57%) received a “fair” rating, and the remaining 11% were rated “poor.” The distribution of quality ratings varied across interventions. For example, neither therapeutic interchange nor DUR had any “good” quality articles, whereas at least 40% of tier and prior authorization articles were rated as “good.”

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**Selected Articles for Review**

Based on the selection criteria described above we reviewed 62 unique articles, representing 7 step therapy studies, 9 prior authorization studies, 27 tiered formulary studies, 5 therapeutic interchange studies, 4 DUR studies, and 11 MTM studies (1 study addressed both a tiered formulary and step-therapy intervention).

**Reviewing the Literature**

The 62 articles that were included in the review were read, reviewed, and summarized by 1 of authors (Shoemaker, Pozniak, Subramanian) using a common data collection template designed to capture key features of the reviewed studies and informed, in part, by the items in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist. Reviewers used the template to capture key points from all articles, regardless of the intervention (e.g., study objectives, setting, participants, study design, limitations). There was also a section on the template designated for capturing specific details of the intervention(s) as appropriate (e.g., drug class(es), intervention groups). To ensure inter-reader reliability, 2 articles on tiers using different methodologies were read and summarized by each of the 3 reviewing authors. The group of readers compared the completed templates for consistency and resolved any discrepancies, which were primarily on the level of detail provided, before reviewing the remaining articles.

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**Appendix I: Detailed Methods**

** Exhibit 2: PubMed Search Results for 1/1/00-12/31/09 [search conducted on 1/6/10]**

<table>
<thead>
<tr>
<th>Search No.</th>
<th>Search Terms</th>
<th>Returned Results</th>
<th>Articles Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Managed Care Programs” [MeSH] or “health maintenance organization” or “preferred provider organization”</td>
<td>12,194</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>“Outcome” or “effect” or “intervention” or “comparison” or “evaluation”</td>
<td>2,130,719</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>#1 and #2</td>
<td>3,525</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Step therapy or “step therapy”</td>
<td>21,514</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>#3 and #4</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>“Medication Therapy Management” [MeSH] or “medication therapy management”</td>
<td>253</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>#3 and #6</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>“Drug Utilization Review” [MeSH] or “drug utilization review” or “drug use evaluation”</td>
<td>1,801</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>#3 and #8</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>Prior authorization or “prior authorization”</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>#3 and #10</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>12</td>
<td>“therapeutic interchange” or “therapeutic substitution”</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>#3 and #12</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>14</td>
<td>“Tier” or “tiers” or “tiered” or “3-tier” or “three-tier” or “tiered formulary” or “3-tier formulary”</td>
<td>2,476</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>#3 and #14</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td><strong>Total Scanned:</strong></td>
<td></td>
<td><strong>143</strong></td>
<td></td>
</tr>
</tbody>
</table>

prescribing practices identified from DUR; however, these studies did not meet the objective of understanding the effect of DUR itself and were therefore excluded. Hence, we identified few articles for review.
### Appendix I: Detailed Methods

#### 3 Criteria Used to Rate Literature of Managed Care Pharmacy Tools

<table>
<thead>
<tr>
<th>Quality Rating</th>
<th>Methodological Rigor</th>
<th>Mitigating Factors that Moved an Article Up or Down</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td>• Experimental (RCT)</td>
<td>• Shorter follow-up periods of time will move “good” articles into “fair”</td>
</tr>
<tr>
<td></td>
<td>• Quasi-experimental (i.e., without randomization). This includes:</td>
<td>• Very small sample size will move “good” articles into “fair”</td>
</tr>
<tr>
<td></td>
<td>• Difference-in-difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Propensity scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Controlled observational studies. This includes:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Case-control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cohort study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Observational studies with unmatched comparison group and with appropriate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sophisticated statistical analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Observational studies with bivariate analysis and with appropriate sophisticated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>statistical analysis</td>
<td></td>
</tr>
<tr>
<td><strong>Fair</strong></td>
<td>• Observational studies without control or comparison group</td>
<td>• Mixed methods will move “poor” articles into “fair”</td>
</tr>
<tr>
<td></td>
<td>• Observational studies with no intervention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Observational studies with unmatched comparison group and without appropriate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sophisticated statistical analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• CEA studies/cost minimization studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Simulation models</td>
<td></td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>• Expert opinion papers</td>
<td>• Mixed methods will move “poor” articles into “fair”</td>
</tr>
<tr>
<td></td>
<td>• Thought papers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Summary papers of other article’s finding (note that the original article may have</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a better rating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Time and motion studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Strictly descriptive analysis (e.g., mean, mode, range, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

*CEA = cost-effectiveness analysis, RCT = randomized controlled trial.*