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RESEARCH NOTES

Potential cost savings by prevention of adverse drug events with a novel medication review program

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ABSTRACT

Objectives: Preventable adverse drug events (ADEs) account for appreciable health care costs and patient morbidity and offer an attractive opportunity for health care providers to improve patient care and decrease costs. It has been suggested that pharmacist intervention can prevent admissions and readmissions due to ADEs. This study assessed the ADEs prevented through a novel medication review program, then estimated the potential cost savings of the prevented ADEs using the literature on cost and prevalence of ADEs that were treated.

Methods: An innovative pharmacist-run medication review was implemented in 2 pharmacies from November 2016 to July 2017. Patients with diabetes, chronic obstructive pulmonary disease, congestive heart failure, prior myocardial infarction, or stroke were included. Pharmacists recorded information about each potential ADE prevented using a standard tracking form which was de-identified and retrospective cost analysis was conducted. Estimates of ADE cost and prevalence requiring treatment were extracted from the literature and incorporated into a model to estimate the potential savings in prevented ADEs overall and per patient. Because ADE costs vary with severity, ADEs in this study were scored for potential severity.

Results: This study included 436 patients with a total of 272 likely and 385 likely or possible ADEs identified. ADEs prevented resulted in an estimated total potential savings of $94,832 (sensitivity analysis [SA]: $2261-$828,921) for likely ADEs and $138,914 (SA: $13,520-$264,308) for likely and possible ADEs. Per patient estimated medication review savings were $218 (SA: $5-$1901) for likely ADEs and $319 (SA: $31-$606) for likely and possible ADEs. The benefit of potential cost savings from providing this medication review was 3.6-5.3 times the pharmacists' time and salary cost.

Conclusions: Pharmacists in this study identified a numerous potential ADEs. By intervening to prevent these ADEs, pharmacists could generate substantial cost savings.

Background

Preventable adverse drug events (ADEs) account for appreciable health care costs and patient morbidity. Preventable ADEs result from injury due to the use of a medication and can result from errors at any stage of medication use. ADEs are classified on the basis of severity as either significant (e.g., rash, nausea/vomiting or diarrhea), serious (e.g., gastrointestinal tract bleed, altered mental status, decrease in blood pressure, allergic reaction, or additional clinic visit), life threating (e.g., intensive care unit admission, intubation, or anaphylaxis), or fatal.[1,2] Common prescriber errors resulting in ADEs include overprescribing medications without an indication, prescribing suboptimal medications, and underprescribing indicated medications. Patient-related factors include nonadherence to prescribed medications.[2] Pharmacist-related factors include errors in labeling, dispensing wrong drug or dose, and insufficient communication with the patient.

Incidence of ADEs in the inpatient setting has been extensively studied with risk factors including polypharmacy, age,

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Key Points

Background:

- Adverse drug events (ADEs) account for appreciable health care costs and patient morbidity.
- Pharmacist intervention can prevent admissions and readmissions due to ADEs.
- This study assessed ADEs prevented through a novel pharmacist-run medication review program in 2 pharmacies and estimated the potential cost savings and benefit to cost ratios of the prevented ADEs.

Findings:

- A model to estimate potential cost savings in prevented ADEs overall and per patient was developed from recorded information on potential ADEs and estimates of ADE-related cost and prevalence requiring treatment from the literature.
- ADEs prevented resulted in an estimated total potential savings of $94,832 (sensitivity analysis [SA]: $2261-$828,921) for likely ADEs to $138, 914 (SA: $13,520-002264,308) for likely and possible ADEs. Estimated per patient medication review savings were $218 (SA: $5-$1901) for likely ADEs and $319 (SA: $31-$606) for possible and likely ADEs. The benefit of potential cost savings from providing this medication review were 3.6-5.3 times the pharmacist's time and salary cost.
- Pharmacists in this study identified a substantial number of potential ADEs, and by intervening to prevent these ADEs, pharmacists could generate substantial cost savings.

sex, length of time since starting a new medication, and hospital site.[2-6] A study published in 1997 reported associated costs of $4685 per preventable ADE and estimated, annual preventable costs for a 700-bed teaching hospital to be $2.8 million.[7] In 2012, Hug et al.[8] reported increased costs of $3511 for each preventable ADE, with higher associated costs for more severe ADEs. Because of the apppreciable cost and patient morbidity burdens, various programs have been attempted to address ADEs in the hospital, including medication safety programs and ADE alert systems.[9-11] Unfortunately, substantially less data on ADE rates and costs exist in the outpatient setting. Risk factors of preventable ADEs in the ambulatory setting are similar to those in the hospital setting and include being female; age 80 years and older; and use of various medications including nonopioid analgesics (nonsteroidal anti-inflammatory drugs and acetaminophen), anticoagulants, diuretics, and antiseizure medications.[12] ADE rates reported in ambulatory care–based studies are lower than those reported in hospital-based studies, probably because patients are in less acute disease states; however, outpatient ADEs are still a notable risk to patient safety.[13] In a systematic review, Taché et al.[13] suggest that approximately 20.1% of all patients taking medications on an outpatient basis experience an ADE, and between 16% and 41.5% of these ADEs are preventable. Gurwitz et al.[14] reported that 27.6% of ADEs in the ambulatory setting were preventable, and 42.2% of these preventable ADEs were categorized as serious, life threatening, or fatal. In addition, there are fewer examples of programs that have been implemented in the outpatient setting to address ADE prevention.[15] Although it is estimated that the prevalence of ADEs in the outpatient setting is less than that in the hospital, there is still a notable cost burden. In 2005, a retrospective cohort study of Medicare patients estimated that the annual costs related to preventable ADEs in the ambulatory setting was $27,365 per 1000 older adults.[16]

Preventing ADEs is an attractive option to improve patient care and decrease health care–related expenditures. The few programs that have been attempted in the community to address ADEs mainly include outpatient electronic health record screening.[15] It has been suggested that pharmacist intervention in the community and in ambulatory care centers can prevent admissions and readmissions due to ADEs.[2] Intervention in chronic disease management and comprehensive medication reviews conducted by trained pharmacists have shown significant benefits. In addition, pharmacists are in the position to be the first health professionals to identify potential ADEs.[17]

One method pharmacists in the community use to manage patient medications and identify medication errors and potential ADEs is a common pharmacy practice service, the traditional brown bag medication review. The shortfalls of the brown bag medication review are 3 fold. First, pharmacists cannot legally throw away expired or no longer indicated patient medications and must return them to the patient. This often leads to patient confusion, as their expired or no longer used medications are mixed with their active therapy regimen. Second, there is no formal consistency or standardization of the service. Finally, there is no formal monitoring or documentation of pharmacist interventions. An innovative program developed by Health Quality Innovators, the recent Center for Medicare Services Quality Innovation Network-Quality Improvement Organization for the states of Virginia and Maryland, elevates the brown bag medication review by "turning it blue." The Blue Bag Initiative was developed with the intent of creating a flexible program that could be used in different health care settings, increase the consistency of data collection on identified potential ADEs, and increase patient engagement through understanding and empowering the management of their medications. This new program provides patients a free blue bag for all medications with a separate small white bag, in which pharmacists isolate inappropriate or expired medications. By physically removing inappropriate or expired medications from the patient's current regimen, pharmacists are able to clearly identify medications for disposal. Moreover, for this study, pharmacists were given a standard tracking form (Supplemental Figures 1 and 2) to document demographic information, chronic disease states, current medications, and potential and actual drug-related issues encountered during the medication review.

Objectives

Implementation of pharmacist-led programs have not estimated potential cost savings for prevented ADEs. The

Table 1
Types of adverse drug events detected[1]

Adverse drug events detected	Causality level[a]	Likely and possible		Likely	
		Count	% (n = 385)	Count	% (n = 272)
Duplicate medications	Likely	42	11%	42	15%
Expired medications	Possible	11	3%	—	—
Contraindication for ≥ 1 medication	Likely	3	1%	3	1%
Drug-drug interaction	Likely	35	9%	35	13%
Medication correct, dose was not	Likely	95	25%	95	35%
Patient stopped taking prescription medications without telling a clinician	Likely	23	6%	23	8%
Patient stopped taking an over-the-counter medication/supplement without telling a clinician	Possible	6	2%	—	—
Patient started new medication prescribed by another doctor without telling a clinician	Possible	22	6%	—	—
Patient started a new over the-counter-medication/supplement without telling a clinician	Possible	27	7%	—	—
Tablet bottles did not match medication list	Possible	47	12%	—	—
Patient not taking medications as prescribed	Likely	33	9%	33	12%
Patient failed to get medication(s) refilled	Likely	41	11%	41	15%
Participant changed to cheaper medication	Not Likely	—	—	—	—
A possible risk to participant safety	Not Likely	—	—	—	—

Abbreviation used: ADE, adverse drug event.
[a] Note: Causality level: identified ADEs were classified as "likely," "possible," and "not likely" to result in actual ADEs based on published classifications of ADEs.[1] Two count versions of ADEs were produced: (1) "likely and possible" and (2) "likely" (for more conservative cases).

purpose of this study was to estimate the economic value of pharmacist-prevented ADEs using deidentified data on potential ADEs prevented, along with published data on costs, consequences, and severity of ADEs, accrued by the Blue Bag Initiative.

Methods

Blue Bag Initiative

The Blue Bag Initiative was conducted for high-risk patients at 2 mid-Atlantic community pharmacies from November 2016 to July 2017. Methods for conducting the program have been previously described.[18] One pharmacy used the program as a follow-up with patients who had received diabetes counseling as a way to re-engage patients. The second pharmacy used the program during home visits, where the pharmacist followed up with the patient monthly to engage the patient and improve adherence. Although the reasons to conduct the program were different, the process of reviewing medications and the standard tracking forms for these reviews were identical (Supplemental Figures 1 and 2). In addition, both pharmacies targeted geriatric patients with chronic disease states and multiple medications. This study was approved by the Virginia Commonwealth University Institutional Review Board.

ADE identification

Retrospective analysis of deidentified tracking forms was conducted, and documented ADEs were compiled from each participating pharmacy. We first classified each of the identified ADEs as "likely," "possible," and "not likely" (Table 1) to correspond to actual ADEs based on the published classifications of ADEs.[1] We then constructed counts of 2 versions of ADEs detected and described them further in Table 1. First, likely and possible ADEs were summed into 1 version, and for a more conservative case, only those ADEs that were likely were counted.

Severity scoring

Methods for scoring severity of ADEs have been previously reported.[1,15,19] Pharmacists who participated in the administration of the Blue Bag Initiative scored the severities of deidentified ADEs from the pharmacy in which they were not employed and for patients whom they did not provide the Bag Initiative service. Pharmacists used guidelines stated by Morimoto et al.[1] and Gandhi et al.[15] (severity levels: fatal, life threatening, serious, and significant) with adjustment of 2 additional categories of "more information needed" and "patient discontinued or omitted" to score severities of identified ADEs (Supplemental Table 1). At least 2 pharmacists estimated the potential severity of each of the ADEs.[1,15] Inter-rater scores were calculated independently for both pharmacies using SPSS Statistics for Mac, Version 25.0 (Released 2017; IBM Corp, Armonk, NY). Inter-rater reliability was calculated using Cohen's κ, for which a score of 0 indicates little reliability of agreement and a score of 1 indicates almost perfect reliability of agreement. Interrater agreement was high for the scored severities of ADEs for both pharmacy 1 (κ, 0.993; 95% CI 0.991–0.994) and pharmacy 2 (κ, 0.897; 95% CI 0.836–0.935).

Literature review

MEDLINE was used to extract literature data. A broad search strategy of relevant terms was used to find evidence of ADE prevalence and associated costs. Initial search strategy was as follows: ("Costs and Cost Analysis"[Mesh]) OR ("Prevalence"[Mesh])) AND (("Drug-Related Side Effects and Adverse Reactions"[Mesh]) OR ("Contraindications, Drug"[Mesh]) OR ("Drug Interactions"[Mesh]) OR ("Medication Adherence"[Mesh]) OR ("Potentially Inappropriate Medication List"[Mesh]) OR ("Medication Therapy Management"[Mesh]) OR ("Medication Reconciliation"[Mesh]) OR ("Medication Errors"[Mesh])) AND (("Outpatients"[Mesh]) OR ("Ambulatory Care"[Mesh]) OR ("Emergency Service, Hospital"[Mesh])) AND (("Adult"[Mesh]) OR ("Aged"[Mesh]) OR ("Aged, 80 and

Table 2
Base cases[a] for cost savings because of blue bag initiative

Base case	# ADEs detected	Prevalence of ambulatory ADEs resulting in harm[13] (%)	Increased cost owing to ADE[16] ($)	% ADEs resulting in admission[21]	Potential cost of ADEs resulting in admission[21] ($)	% ADEs not resulting in admission[21]	Potential cost of ADEs not resulting in admission[21] ($)	Potential, total ADE cost prevented ($)	Potential total ADE cost prevented per patient ($)
Base case A[b]	272	12.8	2819	—	—	—	—	98,142	225
Base case B[c]	385	12.8	2819	—	—	—	—	138,914	319
Base case C[d]	272	12.8	—	31.3	7873	68.7	378	94,832	218
Base case D[e]	385	12.8	—	31.3	7873	68.7	378	134,229	309

Abbreviation used: ADE, adverse drug event.
[a] Note: A base case scenario in an economic model indicates the model with the values of inputs that the researchers believe are most accurate.
[b] Field et al.[16] cost data and conservative likelihood ("likely" only) of ADE occurrence.
[c] Field et al.[16] cost data and less conservative likelihood ("likely and possible") of ADE occurrence.
[d] Hafner et al.[21] cost data and conservative likelihood ("likely" only) of ADE occurrence.
[e] Hafner et al.[21] cost data and less conservative likelihood ("likely and possible") of ADE occurrence.

over"[Mesh])) AND Humans[Mesh] Filters: Humans. The search resulted in 161 articles, from which titles and abstracts were assessed for inclusion and exclusion criteria. Articles were included if they assessed multiple disease states and multiple types of ADEs. Articles were excluded if ADEs did not occur in the outpatient or ambulatory setting. In addition, articles describing programs to address ADEs were excluded. Moreover, articles were pulled from the reference lists of resulting literature.

Resulting ADE-related cost and prevalence of ADEs causing harm extracted from the literature (summarized in Supplemental Table 2) are presented in Table 2 and Table 3 and were incorporated into a model (Figure 1) to estimate potential cost savings for prevented ADEs for the sample and per patient. All cost data were inflated to 2017 dollars with the Bureau of Labor Statistics Consumer Price Index Calculator.

Model building

Figure 1 describes the model flow. Taché et al.[13] reported a 12.8% prevalence of ADEs in the ambulatory setting that resulted in harm and required further medical care. Therefore, we used this prevalence to calculate the percent of ADEs from our sample that may result in appreciable costs down the road if not prevented. Two different paths were then created in the model according to the prevalence of ADEs in the ambulatory setting that resulted in harm. Each path produced 2 base case scenarios (a base case scenario in an economic model indicates a model with the values of inputs which the researchers believe are the most accurate). The first base case was based on Field et al.[16] cost data that indicated the increased cost resulting from 1 ADE to be $2819 in 2017 dollars. The second base case used data from the study by Hafner et al.[21] on the percent of ADEs presenting to emergency departments from the outpatient setting that resulted in admission or without respective associated costs. For each of these base cases, a subsequent case was created for both conservative (cases A and C) and less conservative (cases B and D) likelihoods of ADE occurrence (Table 2). The conservative cases included only those ADEs that were judged to be likely; the less conservative cases included ADEs that were judged to be either likely or possible. Sensitivity analysis (SA) was performed for the base case models (Table 3) to assess the robustness of our resulting estimates. SA is used to test the sensitivity of the results to uncertainty or variation in the values of the input variables. This is necessary because most models are based on estimates that are uncertain or variable. For example, in our model, Field et al.'s data estimated the mean cost of an ADE to be $2819.[16] However, the 95% CI for this estimate was $274-$5763 in 2017 dollars.[16] An SA runs the model with the lower end of the range of estimates, then with the higher end to see to what extent variations in the input variables affect the final result (in our case the potential savings from preventing ADEs with the Blue Bag Initiative). In our SA, we varied the value of a prevented ADE using the 95% CI reported in the estimates by Field et al. and Hafner et al.[16,21] The SA is shown in Table 3.

Cost-benefit analysis

A cost-benefit analysis was conducted from the potential cost savings estimates from the model described above. Inputs of costs for the analysis included pharmacist salary (pharmacists reported a $53-$65 hourly range for conducting the blue

Table 3
Sensitivity analysis for each estimate of cost savings resulting from the blue bag initiative

Base case[a]	ADEs detected	Prevalence of ambulatory ADEs resulting in harm[13] (%)	Increased cost owing to ADE[16] ($)	% ADES resulting in admission[21]	Potential cost of ADE resulting in admission[21] ($)	% ADES not resulting in admission[21]	Potential cost of ADE not resulting in admission[21] ($)	Potential total ADE cost prevented ($)	Potential total ADE cost prevented per patient ($)
Base case A[b]	**272**	**12.8**	**2819**	—	—	—	—	**98,142**	**225**
Low-end case A	—	—	274	—	—	—	—	9552	22
High-end case A	—	—	5363	—	—	—	—	186,732	428
Base case B[c]	**385**	**12.8**	**2819**	—	—	—	—	**138,914**	**319**
Low-end case B	—	—	274	—	—	—	—	13,520	31
High-end case B	—	—	5363	—	—	—	—	264,308	606
Base case C[d]	**272**	**12.8**	—	**31.3**	**7873**	**68.7**	**378**	**94,832**	**218**
Low-end case C	—	—	—	—	139	—	31	2261	5
High-end case C	—	—	—	—	66,059	—	4559	828,921	1901
Base case D[e]	**385**	**12.8**	—	**31.3**	**7873**	**68.7**	**378**	**134,229**	**308**
Low-end case D	—	—	—	—	139	—	31	3200	7
High-end case D	—	—	—	—	66,059	—	4559	1,173,289	2691

Abbreviation used: ADE, adverse drug event.

[a] Note: A base case (bolded) scenario in an economic model indicates the model with the values of inputs which the researchers believe are most accurate. Low end and high end are lower and upper estimates of increased cost owing to an ADE.

[b] Field et al.[16] cost data and conservative likelihood ("likely" only) of ADE occurrence.

[c] Field et al.[16] cost data and less conservative likelihood ("likely and possible") of ADE occurrence.

[d] Hafner et al.[21] cost data and conservative likelihood ("likely" only) of ADE occurrence.

[e] Hafner et al.[21] cost data and less conservative likelihood ("likely and possible") of ADE occurrence.

bag medication reviews) with a 30% fringe benefit and pharmacist time for each patient medication review. Considering the complexity of the medication list, a number of pharmacist identified issues that needed addressing, patient engagement, and answering patient questions and documentations, pharmacists estimated that 20-75 minutes were required per patient medication review. Dividing pharmacist cost per hour by pharmacist time resulted in a range of pharmacist cost per medication review of $23-$106. For this analysis, $61 was used as the average pharmacist cost per medication review. A benefit-cost ratio (BCR) was calculated by dividing the potential cost savings estimated from the model (benefit) by the estimated cost for the pharmacist providing the medication review (Table 4). An SA was performed to determine BCR using the lowest potential cost savings and pharmacist cost per medication review and BCR using the highest potential cost savings and pharmacist cost per review.

Results

ADEs identified and potential cost savings

This study included 436 geriatric, mostly female patients with various chronic disease states and associated complex medication lists (Supplemental Table 3). We identified a total of 272 ("likely") and 385 ("likely and possible") potential ADEs. On average, 0.62 ± 0.8 (mean ± SD) likely and 0.88 ± 1.1 likely and possible ADEs per patient were identified with a range of 0-5 ADEs per patient. The most common ADE detected in either estimate was correct medication with an incorrect dose (Table 1). The next most common ADEs detected (in order per likely and possible, ≥ 9% prevalence) were prescription bottles not matching the recorded medication list, duplicate medications, failing to get medications refilled, drug-drug interactions, and patients not taking medications as prescribed. The least detected ADE (1%) was a contraindication for at least 1 medication.

Pharmacists had almost a perfect agreement in severity scoring. For pharmacy 1 and 2, κ was 0.993 and 0.987, respectively, (a κ between 0.8 and 1.0 indicates near-perfect agreement).[20] Of the ADEs detected, most could not be assessed owing to insufficient information (68.9%-69.1% at pharmacy 1). However, ADEs without enough information were from only 1 of the 2 pharmacies with the same 2 raters. Of those with enough information to be assessed, most were classified as significant (16.5%-17.1% at pharmacy 1 and 82.2%-89.0% at pharmacy 2). There were few serious (12.7%-13.5% at pharmacy 1 and 4.1%-12.3% at pharmacy 2) and life-132#threatening ADEs (1.1% at pharmacy 1 and 5.5%-6.8% at pharmacy 2). Severity scores are further described in Supplemental Table 4.

In the base case analysis, pharmacist identification of ADEs resulted in an estimated total potential savings of $94,832 for likely ADEs and $138,914 for likely and possible ADEs. Estimated saving per patient medication review was $218 for likely ADEs and $319 for possible and likely ADEs (Table 2). The SA indicated a range of $2261-$828,921 of total potential savings from both the pharmacies during November 2016 to July 2017 (9 months) and $5-$1,901 of potential savings per patient (Table 3).

Cost-benefit analysis

Per patient medication review, estimated savings of $218 for likely ADEs and $319 for possible and likely ADEs (Table 2)

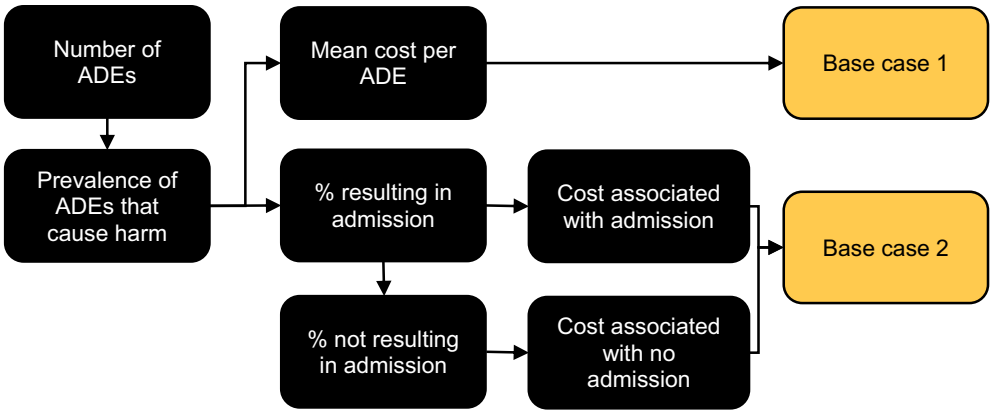

Figure 1. Cost estimate model. Abbreviation used: ADEs, adverse drug events.

were used in a cost-benefit calculation to determine BCR. Accounting for pharmacist salary, fringe benefits, and time to conduct the medication reviews, the potential cost savings estimates resulted in a BCR of 3.6 (range, 2.0-9.5) for base case C (potential cost savings of $218 per medication review from Hafner et al.[21] cost data and likely-only ADE occurrence) and 5.3 (range, 3.0-13.9) for base case B (potential cost savings of $319 per medication review from Field et al. cost data and likely and possible ADE occurrence).[16] This result suggests that the benefit of providing this medication review may be 2-13.9 times the cost. To determine the lowest and highest BCR possible, potential cost savings were used from the SA of the model (Table 3). The lowest benefit with the lowest cost resulted in a BCR of 0.2, whereas the highest benefit at the highest cost resulted in a BCR of 18.

Discussion

This study identified appreciable potential cost savings from intervention via a novel medication review program. With ever rising health care costs and increasingly complex patient needs, managing medication regimens to prevent ADEs is important to prevent downstream morbidities and costs. In a high-risk population, implementation of the Blue Bag Initiative identified ADEs that likely required individual patient-level management. From the results of this study, inaccurate medication dose was the most commonly cited ADE. Pharmacists are highly trained and relied on to make dosing adjustments, notably in inpatient settings and with patient-level renal adjustments. The findings of this medication review program support the increased use of pharmacists as a part of the interprofessional care team in the ambulatory setting. In addition, other ADEs that were detected (more than 10%) concerned areas that pharmacists are uniquely trained to address, including resolving duplicate medications, drug-drug interactions, and adherence. It has been shown that among patients who experience an ADE resulting in an emergency department visit, patients who are nonadherent to their medications have higher health service use for 6 months following the visit.[22] Pharmacists making interventions in patient medication adherence at this stage, before an ADE occurs, would likely have an even greater impact on preventing morbidity and costs downstream.

It was encouraging that the program only detected a few medication contraindications. Although it is possible that pharmacists missed potential contraindications, it is more likely that contraindications are more closely monitored by other providers in clinic, hospital, or other settings within the health care setting, resulting in their lower prevalence compared with other ADEs identified through this study. In addition, the severity of ADEs corresponded with reported trends in the ambulatory setting, as there were more significant ADEs identified compared with serious and life-threatening ADEs.[23]

Implementation of this program resulted in total potential savings of $94,832-$138,914 for the 436 patients screened and

Table 4
Cost-benefit analysis

Case	Benefit ($)	Benefit information	Cost ($)	Cost information	BCR
Scenario 1	218	Base case C[a] (Table 2)	61	Average pharmacist cost per medication review	3.6
			23	Low-end pharmacist cost per medication review	2.0
			106	High-end pharmacist cost per medication review	9.5
Scenario 2	319	Base case B[b] (Table 2)	61	Average pharmacist cost per medication review	5.3
			23	Low-end pharmacist cost per medication review	3.0
			106	High-end pharmacist cost per medication review	13.9
Sensitivity analysis					
Low end[c]	5	Table 3	23	Low end	0.2
High end[c]	1901	Table 3	106	High end	18

Abbreviation used: BCR, benefit-cost ratio.
[a] Note: Hafner et al.[21] cost data and conservative likelihood ("likely" only) of ADE occurrence.
[b] Field et al.[16] cost data and less conservative likelihood ("likely and possible") of ADE occurrence.
[c] Low end and high end are lower and upper estimates, respectively, of increased cost per patient owing to an ADE.

of $218-$319 per medication review. In addition, the benefit of potential cost savings from the cost-benefit analysis of providing this medication review may be 3.6-5.3 times the pharmacists' time and salary cost. This study is the first to estimate potential savings resulting from ADEs that were prevented by pharmacist action alone. The fact that there are potential savings available from ADE prevention with the Blue Bag Initiative may provide incentives for setting a standardized process for conducting medication reviews. The Blue Bag Initiative is already being used in other settings including home health agencies collaborating with pharmacists, in data collection for Medicare enrollment platforms, as a part of team-based chronic care management partnerships between community pharmacists and primary care physicians, and at time of admission (preplanned) into facilities (e.g., skilled nursing facilities and long-term care). However, pharmacists are not reimbursed for preventative care programs such as the Blue Bag Initiative, and payers should consider reimbursement for this potentially cost-saving preventative care.

Limitations

Estimates of the costs of ADEs taken from the literature were wide ranging ($31-$66,059), which led to highly variable estimates in our study.[21] However, our estimates of ADE-related costs overall and per review using different methods and data sources were remarkably similar. For example, the conservative estimate (using only ADEs that were likely to occur) of total costs related to ADEs prevented using Field et al.'s data was $98,142 versus $94,382 using Hafner et al.'s data.[16,21] This increases our confidence in the validity of our estimates.

The prevalence estimates of ADEs in the ambulatory setting that result in harm and require further medical care were representative of the U.S. ambulatory population, whereas the population in this study was likely at a high risk of ADEs and of more severe ADEs owing to its underlying diseases states, age, and rate of polypharmacy. Thus, the reported prevalence of 12.8% of ADEs in the ambulatory setting that require further medical care may underestimate the prevalence in our sample of patients.

Results were based on samples from 2 independent community pharmacies, and it is possible that patient populations in other pharmacies could have appreciable differences. ADE-related variations in costs in the literature often reflect severity. To the best of our ability, we attempted to address this by having pharmacists who participated in Blue Bag Initiative medication reviews clinically assess the severity of the identified potential ADEs. The assessed severities corresponded to those previously published in the literature. However, we were not able to reflect severity in our cost estimates owing to a lack of information about ambulatory costs of ADEs based on severity. We did, however, use median costs per ADE, which include all severities of ADEs in the study population. Assuming that the distribution of potential ADEs by severity in our sample was similar to that of the ADE cost data, we would expect similar cost estimates.

There was considerable heterogeneity of medications and disease states analyzed in this study. If the medications and disease states had been confined to 1 type and/or 1 disease or condition, the results probably would be more consistent and the SA boundaries might be narrower. However, doing so would have substantially reduced our sample size.

We observed differences in the use of the Blue Bag Initiative tracking sheets for the assessed severities. Pharmacy 2 more extensively use the comment section, providing more context about each identified ADE. This allowed raters to judge the severity of more ADEs. This observation highlights the importance of standardized documentation with explicit directions and training to complete each medication review reproducibly. Furthermore, no data were collected on the specific actions taken by the pharmacist as a result of identifying an ADE or follow-up to determine the outcome of the ADE. Therefore, an intervention was assumed, and 12.8% of the resulting ADEs were assumed to require medical treatment. Future improvements of this program would include properly documenting clinical interventions by the pharmacists (i.e., what was done about the identified ADE) and what happened to the patient as a result of the interventions.

Conclusion

A pharmacist-led Blue Bag Initiative medication review prevented a substantial number of potential ADEs and, as a result, likely generated appreciable cost savings. These results suggest that public and private third-party payers would find it cost effective to pay community pharmacists to screen geriatric patients with chronic diseases with complex medication lists for potential ADEs. Standardized medication review programs with documentation are vital to assess interventions that pharmacists make in everyday practice. Further research is needed to determine the long-term effects of these interventions on follow-up and downstream cost savings.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.japh.2019.12.004.

References

1. Morimoto T, Gandhi T, Seger A, Hsieh T, Bates D. Adverse drug events and medication errors: detection and classification methods. *Qual Saf Health Care*. 2004;13(4):306–314.
2. Dalleur O, Beeler PE, Schnipper JL, Donzé J. 30-day potentially avoidable readmissions due to adverse drug events [e-pub ahead of print]. *J Patient Saf*. 2017. Available at: https://doi.org/10.1097/PTS.0000000000000346. Accessed March 9, 2018.
3. Hug BL, Witkowski DJ, Sox CM, et al. Adverse drug event rates in six community hospitals and the potential impact of computerized physician order entry for prevention. *J Gen Intern Med*. 2010;25(1):31–38.
4. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. ADE prevention study group. *JAMA*. 1995;274(1):29–34.
5. Laatikainen O, Miettunen J, Sneck S, Lehtiniemi H, Tenhunen O, Turpeinen M. The prevalence of medication-related adverse events in inpatients-a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2017;73(12):1539–1549.
6. Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. *Eur J Clin Pharmacol*. 2018;74(4):389–404.
7. Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. Adverse drug events prevention study group. *JAMA*. 1997;277(4):307–311.
8. Hug BL, Keohane C, Seger DL, Yoon C, Bates DW. The costs of adverse drug events in community hospitals. *Jt Comm J Qual Patient Saf*. 2012;38(3):120–126.

9. Piontek F, Kohli R, Conlon P, Ellis JJ, Jablonski J, Kini N. Effects of an adverse-drug-event alert system on cost and quality outcomes in community hospitals. *Am J Health Syst Pharm*. 2010;67(8):613–620.
10. Cohen MM, Kimmel NL, Benage MK, et al. Medication safety program reduces adverse drug events in a community hospital. *Qual Saf Health Care*. 2005;14(3):169–174.
11. McClead Jr RE, Catt C, Davis JT, et al. An internal quality improvement collaborative significantly reduces hospital-wide medication error related adverse drug events. *J Pediatr*. 2014;165(6), 1222.e1–1229.e1.
12. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc*. 2004;52(8):1349–1354.
13. Taché SV, Sönnichsen A, Ashcroft DM. Prevalence of adverse drug events in ambulatory care: a systematic review. *Ann Pharmacother*. 2011;45(7-8):977–989.
14. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA*. 2003;289(9):1107–1116.
15. Gandhi TK, Seger AC, Overhage JM, et al. Outpatient adverse drug events identified by screening electronic health records. *J Patient Saf*. 2010;6(2):91–96.
16. Field TS, Gilman BH, Subramanian S, Fuller JC, Bates DW, Gurwitz JH. The costs associated with adverse drug events among older adults in the ambulatory setting. *Med Care*. 2005;43(12):1171–1176.
17. Cranor CW, Bunting BA, Christensen DB. The Asheville project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. *J Am Pharm Assoc (Wash)*. 2003;43(2):173–184.
18. Twigg G, David T, Taylor J. An improved comprehensive medication review process to assess healthcare outcomes in a rural independent community pharmacy. *Pharmacy (Basel)*. 2019;7(2):66.
19. Hallgren KA. Computing inter-rater reliability for observational data: an overview and tutorial. *Tutor Quant Methods Psychol*. 2012;8(1):23–34.
20. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012;22(3):276–282.
21. Hafner Jr JW, Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. *Ann Emerg Med*. 2002;39(3):258–267.
22. Hohl CM, Nosyk B, Kuramoto L, et al. Outcomes of emergency department patients presenting with adverse drug events. *Ann Emerg Med*. 2011;58(3), 270.e4–279.e4s.
23. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med*. 2003;348(16):1556–1564.

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Supplementary Data

Supplemental Table 1
Severity scoring guidelines (adapted from the studies by Morimoto et al.[1] and Gandhi et al.[15])

Severity	Example
Fatal	• Patient died owing to the incident
Life threatening	• Patient transferred to intensive care unit
	• Respiratory failure requiring intubation
	• Mental status change: patient falls and gets intracranial hemorrhage
	• Tongue swelling/anaphylactic shock due to medication
	• International normalized ratio > 5.0
	• Insulin and seizure
	• Diuretic and hypokalemia
Serious	• Gastrointestinal tract bleed
	• Altered mental status/excessive sedation due to medication
	• Increased creatinine due to medication
	• Decrease in blood pressure
	• Patient feels lightheaded
	• Allergic reaction: shaking chills/fever
	• Additional visit to clinic for treatment
	• Additional medications
	• Steroids and elevated glucose
	• Hypoglycemia and falls
Significant	• Rash
	• Diarrhea due to antibiotics
	• Thrombocytopenia due to histamine type 2 antagonist
	• Nausea and vomiting
	• Any significant event that is identified but the patient does not require a change in therapy
	• Angiotensin-converting enzyme inhibitor and cough
	• Furosemide and renal failure
More information needed	• Not enough information provided
Patient discontinued or omitted	• Patient chose not to participate

Supplemental Table 2
Literature data for prevalence of ADEs requiring treatment and cost of ADEs in the ambulatory setting

Citation	Prevalence (%)	Prevalence information
Taché et al.[13]	12.8	Median prevalence of ADEs in the ambulatory setting that resulted in harm requiring further medical care
Hafner et al.[21]	2.8	Low-end prevalence of ADEs in the ambulatory setting resulting in admission
	34.7	High-end prevalence of ADEs in the ambulatory setting resulting in admission
	68.7	Prevalence of ADEs in the ambulatory setting resulting in no admission

Reference	Cost ($)	Cost information
Field et al.[16]	2818.88	—
	274.35	Low end
	5363.40	High end
Hafner et al.[21]	377.75	No admission
	31.11	Low end
	4559.36	High end
	7873.10	Admission
	139.20	Low end
	$66,058.61	High end

Abbreviation used: ADEs, adverse drug events.

Supplemental Table 3
Pharmacy-specific demographics

Demographic	Pharmacy 1 (n = 363)	Pharmacy 2 (n = 73)
	Mean (SD)	
Age (y)	75.4 (9.8)	65.6 (12)
	Count (%)	
Female	208 (57)	45 (63)
Number of medications	15.7 (5.7, range: 3–34)	9 (3.3, range: 4–14)
Disease state		
Atrial fibrillation	10 (2.7)	3 (1.4)
Atherosclerotic cardiovascular disease	60 (16.4)	34 (15.3)
Cancer	1 (0.3)	1 (0.5)
Congestive heart failure	68 (18.6)	1 (0.5)
Kidney disease	14 (3.8)	4 (1.8)
Chronic obstructive pulmonary disease	36 (9.9)	1 (0.5)
Other respiratory disease	40 (11)	3 (1.4)
Diabetes type 2	5 (1.4)	70 (31.5)
Edema (not because of heart failure)	2 (0.5)	8 (3.6)
Gastrointestinal tract disease	22 (6)	10 (4.5)
Hypertension	9 (2.5)	36 (16.2)
Pain	9 (2.5)	5 (2.3)
Ocular disease	1 (0.3)	2 (0.9)
Osteoporosis	1 (0.3)	11 (5)
Seizure disorder	4 (1.1)	1 (0.5)
Skin disease	8 (2.2)	1 (0.5)
Urinary disease	4 (1.1)	1 (0.5)
Other	71 (19.5)	30 (13.5)

Supplemental Table 4
Severity scores for identified potential adverse drug events

Pharmacy 1 (κ = 0.993)				
Severity	Count pharmacist 1	% (n = 363) pharmacist 1	Count pharmacist 2	% (n = 363) pharmacist 2
SIG	62	17.1	60	16.5
SER	46	12.7	49	13.5
LT	4	1.1	4	1.1
NI	251	69.1	250	68.9
Pharmacy 2 (κ = 0.897)				
Severity	Count pharmacist 3	% (n = 73) pharmacist 3	Count pharmacist 4	% (n = 73) pharmacist 4
SIG	65	89.0	60	82.2
SER	3	4.1	9	12.3
LT	5	6.8	4	5.5
NI	0	0	0	0

Abbreviations used: LT, life threatening; NI, more information needed; SER, serious; SIG, significant.

Medication Review Form

BLUE BAG INITIATIVE

Date: _____

Participant name: _____ Participant #: _____

D.O.B. _____ M ☐ F ☐ Phone #: _____ Zip Code: _____

Participant diagnosis: _____ Location: _____

Race (Check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ African American

☐ Native American or Pacific Islander ☐ White ☐ Other: _____

Person(s) completing form: _____

Please check all that apply: ☐ Medicare ☐ Medicaid ☐ Both ☐ Other Insurance ☐ No insurance

Medication	Route	Dose	Schedule	Indication	Comment

1. How many medications (prescription, over the counter, vitamins/minerals/nutraceutics) were brought by the participant? _____

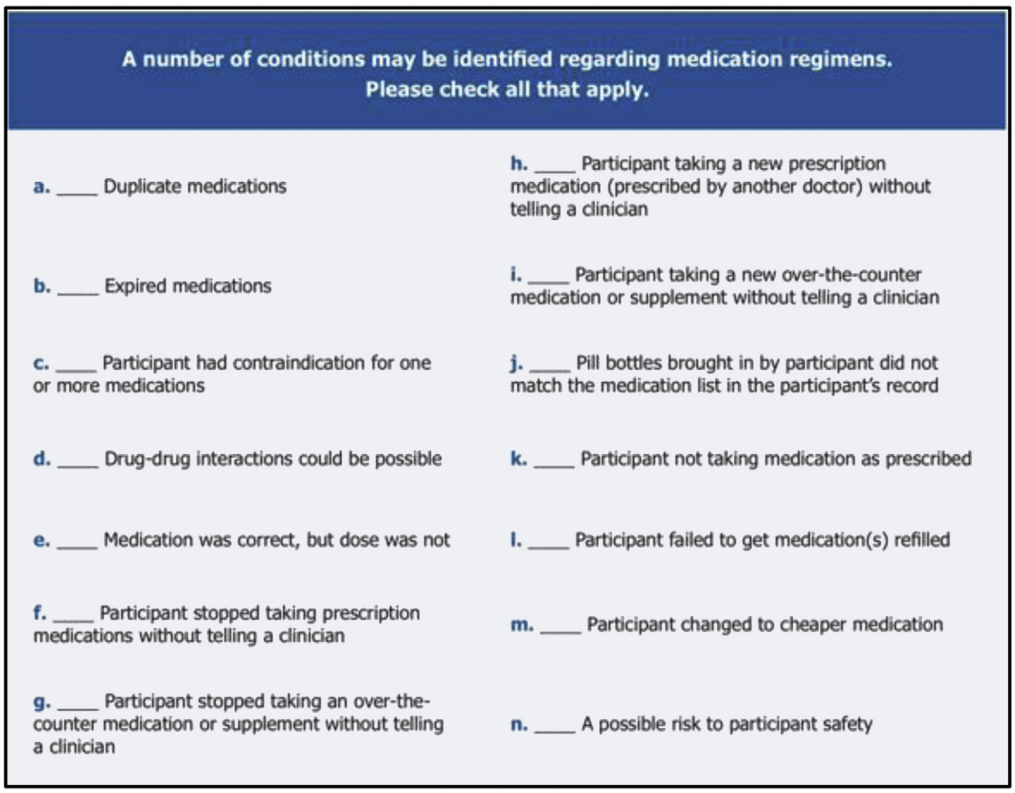
2. Did the participant say they brought in all their prescription medication containers?
   ☐ Yes ☐ No

3. Did the participant say they brought in all their over the counter medications and supplements?
   ☐ Yes ☐ No

4. Has anyone asked about the participants medications in the last 6 months, not including today's discussion? ☐ Yes ☐ No

5. Could the participant state what each medication was for? ☐ Yes ☐ No

Supplemental Figure 1. Blue Bag Initiative standard tracking sheet page 1.



A number of conditions may be identified regarding medication regimens. Please check all that apply.

a. ____ Duplicate medications

b. ____ Expired medications

c. ____ Participant had contraindication for one or more medications

d. ____ Drug-drug interactions could be possible

e. ____ Medication was correct, but dose was not

f. ____ Participant stopped taking prescription medications without telling a clinician

g. ____ Participant stopped taking an over-the-counter medication or supplement without telling a clinician

h. ____ Participant taking a new prescription medication (prescribed by another doctor) without telling a clinician

i. ____ Participant taking a new over-the-counter medication or supplement without telling a clinician

j. ____ Pill bottles brought in by participant did not match the medication list in the participant's record

k. ____ Participant not taking medication as prescribed

l. ____ Participant failed to get medication(s) refilled

m. ____ Participant changed to cheaper medication

n. ____ A possible risk to participant safety

Supplemental Figure 2. Blue Bag Initiative standard tracking sheet page 2.